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LETTER

Fast adjustment of pace-of-life and risk-taking to changes in food quality by altered gene expression in house mice

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Abstract

The pace-of-life syndrome hypothesis provides a framework for the adaptive integration of behaviour, physiology and life history between and within species. It suggests that behaviours involving a risk of death or injury should co-vary with a higher allocation to fast reproduction. Empirical support for this hypothesis is mixed, presumably because important influencing factors such as environmental variation, are usually neglected. By experimentally manipulating food quality of wild mice living under semi-natural conditions for three generations, we show that individuals adjust their life history strategies and risk-taking behaviours as well as trait covariation ($N_{individuals}$ = 1442). These phenotypic differences are correlated to differences in transcriptomic gene expression of primary metabolic processes in the liver while no changes in gene frequencies occurred. Our discussion emphasises the need to integrate the role of environmental conditions and phenotypic plasticity in shaping relationships among behaviour, physiology and life history in response to changing environmental conditions.

KEYWORDS
adaptation, extended pace-of-life syndrome, phenotypic plasticity, risk-taking

INTRODUCTION

A range of life-history strategies along a fast-slow continuum emerge due to trade-offs between allocation to current and future reproduction (Stearns, 1989). Fast organisms gain reproductive maturity quickly and have high fecundity but typically short lifespan. Such organisms prioritise current reproduction against future survival. Slow organisms prioritise survival and usually have a long lifespan, that is, a high survival rate but low fecundity. Life history and physiology have coevolved with respect to the environment (Ricklefs & Wikelski, 2002), implying that environmental conditions favour certain sets of traits over others. Such trait differences are presumably maintained through molecular pathways mediating the interactions between genetic background and environment. Originally, POLS studies focused on investigating life history and physiological traits at the species and population level. Recently, the "extended" POLS hypothesis suggested that behavioural traits should also be considered in POLS studies as they play a significant part in reconciling life history trade-offs (Réale et al., 2010).

The inclusion of behavioural traits in POLS research has shifted the focus of investigation to variation in life history strategies at the individual level (Dammhahn et al., 2018). This brings into focus some additional issues not present at the species or population level. For example, individuals with more resources can have both, high fecundity and long lifespan compared to individuals with fewer resources (Van Noordwijk & de Jong, 1986). Investigation of traits at the individual level requires

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metrics that can be consistently recorded for each individual such as individual fecundity rates (Araya-Ajoy et al., 2018) and generation time (Sæther et al., 2005). The extended POLS hypothesis predicts individuals with high fecundity and short generation times to be consistently more risk-taking, explorative and aggressive, thereby offering an explanation for consistent individual differences in behaviour, that is, animal personality (Réale et al., 2010).

Correlational selection was originally thought to explain correlations between life history, behaviour and physiology. More recently, density-dependent selection via fluctuations in population densities over time has been suggested as a driving factor for POLS (Milles et al., 2022; Wright et al., 2019). Such processes require many generations. Adaptation to changing environmental conditions, however, is often observed much faster, implying a role of plasticity for POLS traits to change. Feedback loops between traits of different domains (Luttbeg & Sih, 2010) or ecological conditions (Montiglio et al., 2018), might affect the associations between traits. Nutrition, especially during development, is well known to affect life history as well as behaviours (Lindström, 1999). Developing under low-quality conditions impairs reproductive capacity in adulthood (Blount et al., 2006) and allocation to parenting strategies (Krause et al., 2017), with persisting effects across generations (Krause & Naguib, 2014). Theoretical considerations recently suggested heterogeneity in resource availability in the environment and/ or in the effects of behaviours in mediating resource acquisition versus allocation to be responsible for the mixed support of the POLS hypothesis (Haave-Audet et al., 2022; Laskowski, Moiron, & Niemelä, 2021).

In this study, we therefore investigate how a change in food quality affects trait patterns predicted by the extended POLS hypothesis. The focus is on testing if life history and consistent behavioural differences, that is, personality traits, of *Mus musculus domesticus* adapt to changes in food quality. Furthermore, we start to explore gene expression changes associated with adaptations to such environmental changes. Specifically, we asked:

1. Does a change in food quality bring about phenotypic differences in life history and personality traits?

1.1. Can variation in food quality produce observable changes in POL? Do animals of high-quality food (HQ) populations mature earlier and emphasise reproduction more than animals of standard-quality food (SQ) populations.

1.2. Do stress-coping and risk-taking adjust to differences in food quality in three generations corresponding to individual POL?

2. What are the possible regulatory mechanisms of the observed phenotypic differences?

2.1. Which gene expression changes do occur in conjunction with the adjustments of POL and behaviours in liver and hippocampus?

2.2. Which molecular pathways are involved in facilitating phenotypic changes?

We released outbred, laboratory-reared descendants of wild mice into two replicate semi-natural enclosures each (N_{total} = 4, two per food quality). Across three generations, we followed individual life history trajectories and measured behavioural traits of individuals. The semi-natural enclosures allowed us to mimic natural conditions very closely (see Supplementary material S1, S3). To our knowledge, this study is the first attempt to test the POLS hypothesis across several generations following a change in the environment. To understand the molecular pathways involved in establishing life history and behavioural trait differences on the two food types, we performed transcriptome analysis in hippocampus and liver. We chose liver as the focal metabolic organ, while the hippocampus releases hormones directly regulating liver function and may also be involved in the manifestation of behaviours.

We predicted populations on HQ food to develop a faster POL based on previous research (Börsch-Haubold et al., 2014). Börsch-Haubold et al. (2014) observed a larger number of offspring produced within similar time in HQ populations as compared to populations on SQ. Based on the extended POLS, we hypothesise that a fast POL under HQ conditions will be associated with an increased risk-taking and a proactive stress-coping behaviour (Réale et al., 2010). We used microsatellite loci to assign parentages and to compare population parameters such as inbreeding coefficients, heterozygosity levels and general population structure across enclosures to rule out that possible effects might be generated by stochastic genetic fluctuations. Finally, we expected transcriptomic profiles and especially gene expression pathways related to metabolic processes, to reflect treatment differences correlated with the observed differences in life history and behaviour.

MATERIALS AND METHODS

Housing and experimental design

First, we determined population growth and carrying capacity of our semi-natural enclosures (Supplementary material S1) and consequently kept the maximum number of mice per enclosure close to but below the carrying capacity.

Founders (N = 160, 80 males, 80 females, originating from 17 families) were laboratory-reared descendants of wild *Mus musculus*. Genetic diversity was maintained by the implementation of an outbreeding regime for 17 generations and by introduction of fresh wild-caught mice in the 8th generation (Harr et al., 2016). Experimental mice were raised under standard laboratory cage conditions and all mice received Standard Diet 1324 (Altromin, Germany) and water ad libitum.

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Mice were released into semi-natural enclosures at~6 months old. 20 males and 20 females founded each population. Families were distributed equally across enclosures and all animals founding one enclosure were unknown to each other.

Four enclosures (17.5–19.5 m^2) were run in parallel for 14 months. Enclosures were littered with wood chips, wood wool and toilet paper. Several structure elements increased environmental complexity. Sixteen shelters and nine feeding and water stations were distributed equally across the enclosure (Supplementary material S2). Enclosures received natural daylight and temperature fluctuations, underfloor heating prevented temperatures to fall below 10°C since mice were not able to dig burrows to escape cold temperatures (Supplementary material S3).

Two enclosures received standard food SQ (Altromin 1324) while the other two received higher quality food HQ (Altromin 1414). The SQ food contained 3227 kcal/kg metabolisable energy (24% from protein, 11% from fat and 65% from carbohydrates) while HQ food contained 3680 kcal/kg (28% from protein, 22% from fat and 50% from carbohydrates). If given the choice, mice preferred the HQ over the SQ food (Supplementary material S6).

After releasing the founders, we monitored population developments every 4–5 weeks. We caught all mice within an enclosure, determined body mass and took a tissue sample of new individuals (weighing >10 g) for parentage assignment. New animals received an RFID pit tag (Planet ID, 1.4 × 9 mm) for permanent recognition.

Microsatellite genotyping

1442 individual samples were typed for 17 unlinked microsatellite loci (Supplementary material S4), using the standard protocol for the QIAGEN Multiplex PCR kit. Alleles were called using GeneMarker (V 3.0.1). Genotyping was done as described in detail in Linnenbrink et al. (2013). We used the allele data to (a) investigate the genetic structure of enclosures across generations, (b) to assign parentages and (c) to determine and exclude mixed-generation individuals for behavioural and transcriptomic analyses.

Enclosure genetics

Frequency estimation of null alleles was done using CERVUS 3.0.7 (Kalinowski et al., 2007). Four loci (Supplementary material S4) had null allele frequencies >5% and were removed from further analyses. Expected and observed heterozygosities and average number of alleles were calculated using CERVUS. The inbreeding coefficient F_{IS} and, for genetic differentiation R_{ST}, was assessed by using ARLEQUIN Version 3.5.2.2 (Excoffier et al., 2005). STRUCTURE Version 2.3.4 (Pritchard et al., 2000) was used to investigate genetic differentiation between the enclosure populations, overall and for single generations F0-F3. We ran STRUCTURE analysis for the number of clusters K = 2–4 and K = 4, to determine substructure according to treatment or enclosure. We assumed admixture for STRUCTURE analysis, as all founder individuals came from the same pool. Parameters used were 2000 burn-in period and 5000 Markov chain Monte Carlo (MCMC) simulations with three iterations per number of clusters.

Parentage assignment

Parentage was determined based on all 17 loci using Colony (V 2.0.6.6., [Jones & Wang, 2010]), using full likelihood, male and female polygyny and potential inbreeding. All mice of reproductive age in any given month were considered potential parents. Parent pairs were adopted if assigned with more than 90% probability.

Behaviours

To trap mice, 20 life traps per enclosure were set up for several hours each evening until enough measurements had been taken for a given trapping session. Trapping started shortly before the onset of the activity period, depending on the season from 3:30–6:30 pm and lasted between 4 and 5 h. Traps were controlled every 10–20 min. To minimise any carry-over effects, each animal conducted only one test per trapping night. A second trapping session was conducted 4 weeks later to re-test individuals.

Open field

Mice were introduced to the middle of a 60 × 60 cm arena for five minutes. We measured the total distance covered and the percentage of time spent 10 cm away from the wall. Behaviours were video recorded and analysed using software VideoMotion2 (TSE).

Novel environment

A 530 × 330 mm cm cage with a transparent lid was placed close to the point of capture of each mouse (i.e. most likely in the territory of the mouse). The cage contained three objects unknown to the mice. Mice could choose to explore this unknown environment for 10 min. The latency to enter the unknown environment from the life trap, the time spent exploring and the number of exploration trips was analysed.

Transcriptomics

After each following generation had grown to at least 60 offspring, we caught a subset of animals from which we had full behavioural and life history data. Animals were immediately sacrificed using CO_2 and dissected within 5 min. A part of the left liver lobe and the left hippocampus were snap-frozen. We selected 10 unrelated individuals (5 per sex) per enclosure and generation for transcriptome analyses.

RNA was extracted using QIAGEN RNeasy Microarray Tissue Mini Kit (Catalogue No. 73304) and sequenced by Novogene based on the Illumina TruSeq Stranded mRNA HT library Prep Kit protocol.

Sequencing outputs were filtered to remove 'degraded' samples and four samples were removed due to mislabelling. Remaining sample reads were trimmed with Trimmomatic (Bolger et al., 2014). Paired-end reads were mapped to the mouse genome GRCm39 with HISAT2 and SAMtools (Consortium et al., 2002, Li & Durbin, 2009, Kim et al., 2015), onto the Ensembl mouse gene annotation (release-104) with hisat2-build options –ss and -exon. We used HTSeq to count fragments mapped to the annotated genes and performed differential expression analysis in R with the DESeq2 library (Love et al., 2014).

Statistical analyses

Life history

For individuals with at least one surviving offspring, we calculated individual fecundity rate as the mean number of new offspring produced per reproductive round of monthly observations:

$$\textit{Individual Fecundity rate} = \frac{\sum \textit{New off spring in each reproductive round}}{\textit{total number of reproductive rounds}}$$

We computed individual generation time as the weighted mean age of the individual when it reproduced:

$$\textit{Individual Generation time} = \frac{\sum \textit{Round of reproduction x new off spring}}{\textit{total number of off spring}}$$

Kruskal–Wallis tests were used to evaluate differences in fecundity rate and generation time for each generation.

Behaviour

We assessed repeatability using the rptR package (Stoffel et al., 2017) calculating univariate mixed models including trial and generation as fixed and individual as random effect. Model assumptions for these and other mixed models were checked by using qq-plots and plotting residual versus fitted values and residual distributions chosen accordingly.

To test for treatment differences across generations, we modelled each repeatable trait using trial, treatment, generation, sex and the two-way interactions between generation, sex and treatment as fixed and individual as well as enclosure identity as random effects. If an interaction involving generation was significant, we analysed the generations separately in more detail.

To test for among-individual correlations, we constructed one Bayesian multi-response model (R package MCMCglmm, [Hadfield, 2010]) containing generation time, fecundity and the repeatable behavioural variables. We assumed a Gaussian distribution for all variables except the number of exploration trips which was modelled assuming a Poisson distribution. We used a slightly informative inverse Wishart prior after centring all means around zero and assuming variances of three to ten times of the actually observed variances per variable. We ran three chains with 525,000 iterations, a burn-in of 25,000 and a thinning interval of 500. These parameters yielded good model conversions across runs (Gelman & Rubin, 1992) and low auto-correlation. Correlations (estimated as the VCV(variable 1: variable 2)/sqrt(VCV(variable 1)*VCV(variable2))) among traits were accepted as significant if the estimated credible interval did not include zero.

Functional assignment of expression data

We performed downstream functional gene ontology enrichment analysis using the overrepresentation test of the PANTHER database (Supplemental section S8).

Ethics statement

All animals were handled and procedures were carried out according to national guidelines. Procedures are approved under licences V244-12767/2019 and V244-31223/2019(62–5/19) by the Ministerium für Energiewende, Landwirtschaftliche Räume und Umwelt, Kiel. Keeping of mice was approved and is regularly controlled by the Veterinäramt Plön under permit: 1401-144/PLÖ-004697.

RESULTS

Food-quality, pace-of-life and behaviours

We tested if animals of HQ populations developed the expected faster POL. Across generations, 44–62% of all females per generation and 32–53% of males reproduced in both treatments. Median individual fecundity rates increased across generations for both sexes on the HQ food (Figure 1a,b). Generation time of females raised on

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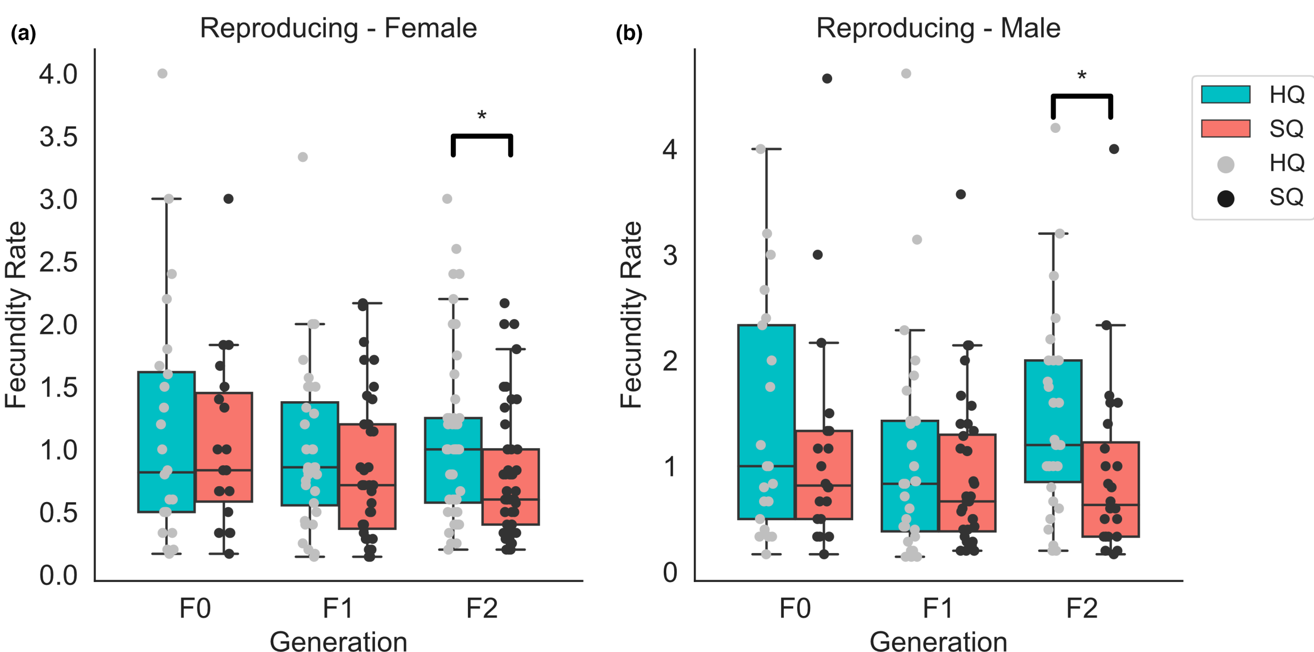

FIGURE 1 Fecundity rates of (a) females that had at least one surviving offspring and (b) males that sired at least one surviving offspring.

HQ food significantly decreased (Figure 2a,b). We observed a similar but non-significant trend in males.

In an additional experiment, we found further evidence for a generally faster POL of HQ animals (Supplementary material S5). Birthing probability and litter size at birth did not differ for SQ and HQ females. However, due to a reduction in litter size, SQ females weaned significantly smaller litters (t = −2.44, p = 0.02, LS at weaning: 3.2) and weaned offspring 5–6 days later than HQ females (t = 3.2, p = 0.006, LS at weaning: 5.5), despite similar body mass. In addition, SQ males needed ~6 days longer than HQ males to reach adult body mass (t = 2.2, p = 0.04) while there was no difference for females (mean developmental time: 77 days).

We then tested if animals express consistent differences in behaviour going along with changes in POL. All behavioural traits were significantly repeatable (Table S2).

The OF centre time showed a significant generation by treatment interaction (F = 4.12, df = 3, p = 0.007) but treatments only differed in the F1 (t = −2.9, p = 0.005) generation. Whether individuals coped with the stressful situation actively or passively was influenced by treatment and generation (F = 8.93, df = 3, p < 0.001, Figure 3). While founders (t = 0.53, p = 0.59) and F1 (t = 1.64, p = 0.10) did not differ, from the F2 generation onwards we found a treatment difference (F2: t = 2.83, p = 0.006; F3: t = 4.73, p < 0.001). The effect sizes increased from one generation to the next (Figure 3). Sexes did not differ in the time spent in the central zone or the distance covered in any generation (all p > 0.09).

The latency to enter a novel environment showed a significant treatment by generation interaction (F = 3.58, df = 3, p = 0.01) but on subsequent analysis only the F3 generation showed a treatment difference (F = 3.2, df = 1, p = 0.04) with HQ animals needing longer to enter. Neither the time spent exploring nor the number of trips showed any treatment effects. For the F0 and F1, females needed longer to enter, spent less time exploring and made fewer trips into the novel environment with sex differences becoming smaller across generations, leading to a non-significant difference in the F2 and F3 generations (Table S3).

Across all generations and both treatments, the two life history variables were not correlated with each other (Table 1). Individuals covering more distance in the open field (i.e. proactive) also had a longer generation time. The fecundity rate was negatively associated with the number of exploration trips. We also found a correlation between OF centre time and both exploration variables (OF-NEexploration: R = 0.42, CI: 0.1–0.68; OF-NETrips: R = 0.41, CI: 0.12–0.73).

Next, we estimated between-individual correlations separately by treatment for F2 and F3 generations since we found significant treatment differences in life history and behaviour for these generations. While the two life history variables correlated negatively in SQ, no correlation was observed in the HQ treatment (Table 1). The correlation between generation time and OF distance was significantly stronger in the HQ compared to the SQ treatment.

Genetic differentiation between enclosures, inbreeding and heterozygosity

We tested if the four enclosures maintained genetic diversity across generations and whether there was any effect of inbreeding or genetic differentiation according to the food treatment by using 13 unlinked microsatellite loci.

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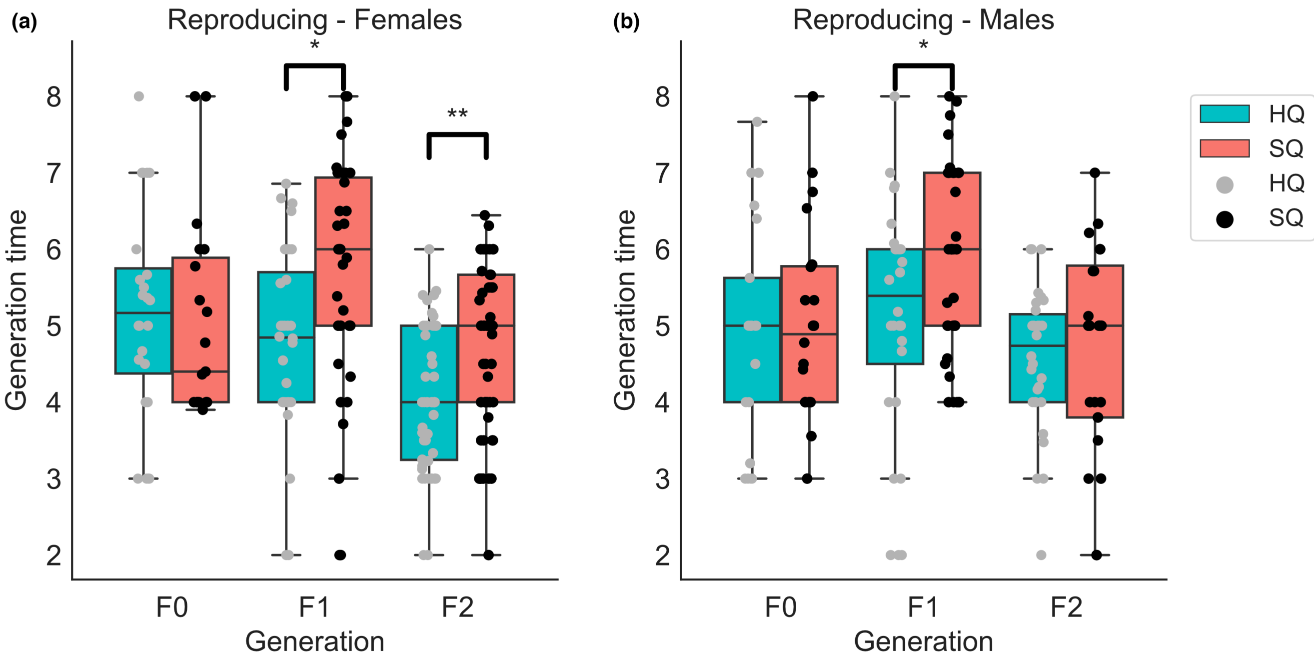

FIGURE 2 Generation times of (a) females that had at least one surviving offspring and (b) males that sired at least one surviving offspring.

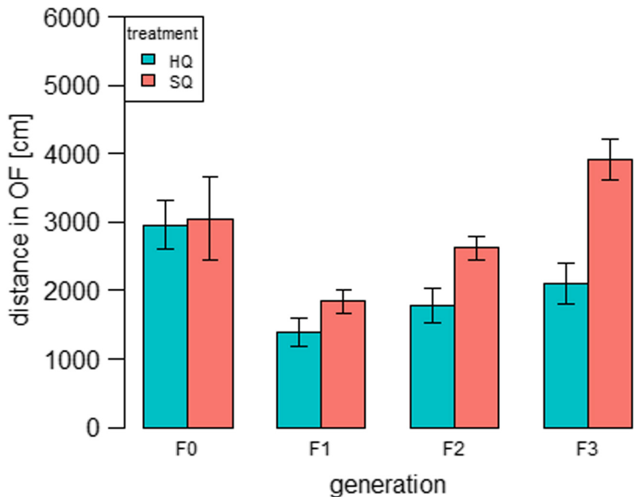

FIGURE 3 Distance covered in the open field from the founding (F0) to the F3 generation

Assuming four potential clusters (K = 4), STRUCTURE results show an equal distribution of all clusters within each room (Figure 4). Further analysis of F1-F3 gives evidence for an ongoing differentiation between the enclosures. However, overall genetic differentiation of all individuals ($n = 1442$) estimated by R_{ST} gives an average of 0.031 (Table S5). Observed heterozygosities were in the range of expected heterozygosities and also F_{IS} showed no signs of overall inbreeding within the enclosures.

Effects on food quality on gene expression patterns

We tested if the observed differences in POL and behaviours correlate with differences in overall gene expression. We performed differential expression analysis for 63 liver and 112 hippocampus samples. Principal component analysis (PCA) of transcriptomes shows the expected clustering based on the tissue type and reveals strong sex differences in liver but not hippocampus samples (Supplementary material S9). In the liver, 2218 genes and in the hippocampus 3440 genes were differentially expressed. However, only 16 genes posited more extreme than $\mp 0.58 \times \log 2$ (>1.5× or <0.5× absolute) fold change in hippocampus, while the corresponding number was 431 in liver and *Srp54a* was the single gene common in both sets. Gene ontology enrichment analysis confirmed that the 431 differentially expressed genes in liver were enriched in metabolic pathway-associated genes (Supplemental material S9).

Due to the observed difference between the liver data from males and females (Figure 5), we further split the liver samples based on sex. The generations showed no significant differentiation. Averaged across generations, 159 and 530 genes were differentially expressed with respect to the food treatment in female and male liver samples respectively. 83 and 219 genes had more extreme than $\mp 0.58 \times \log 2$ fold change in female and male liver samples respectively, and only 11 of these genes were common to both sexes.

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TABLE 1 Between-individual correlation among traits

	All generations	Food-specific correlations		Difference between treatments
Correlation	**Both treatments**	**HQ**	**SQ**	
Fecundity—generation time[a]	R = −0.02, CI: −0.22 -+0.18	R = −0.05, CI: −0.30 -+0.16	**R = −0.38, CI: −0.69 - -0.04**	*
Generation time - OF distance[a]	**R = 0.22; CI: 0.05–0.39**	**R = 0.43, CI: 0.20–0.61**	R = 0, CI: −0.25 -+0.26	*
Fecundity NE trips[a]	**R = −0.18, CI: −0.42 - -0.07**	R = −0.02, CI: −0.38 -+0.27	**R = −0.38, CI: −0.69 - - 0.04**	
Generation time - NE exploration[a]	R = −0.07, CI: −0.19 -+0.18	**R = 0.28, CI: 0.15–0.59**	R = −0.12, CI: −0.60 -+0.36	
Generation time - NE trips[a]	R = 0.04, CI: −0.15 -+0.22	**R = 0.20, CI: 0.05–0.51**	R = −0.14, CI: −0.50 -+0.25	
OF distance - OF centre[b]	**R = 0.48, CI: 0.27–0.68**	**R = 0.45, CI: 0.17–0.73**	**R = 0.40, CI: 0.06–0.67**	
NE exploration - NE trips[b]	**R = 0.85, CI: 0.72–0.93**	**R = 0.87, CI: 0.75–0.97**	R = 0.38, CI: −0.35 -+0.55	*

Note: Correlations with credible intervals that do not include zero are considered significant and highlighted in bold. Food-specific correlations were estimated for F2 and F3 generations after treatment differences emerged. For correlations involving life history variables, only F2 generation is considered (marked with superscript a) while for purely behavioural correlations F2 and F3 generations are included (superscript b).

*Indicate non-overlapping posterior correlations estimates between treatment correlations estimated as: Δr = r(SQ)−r(HQ).

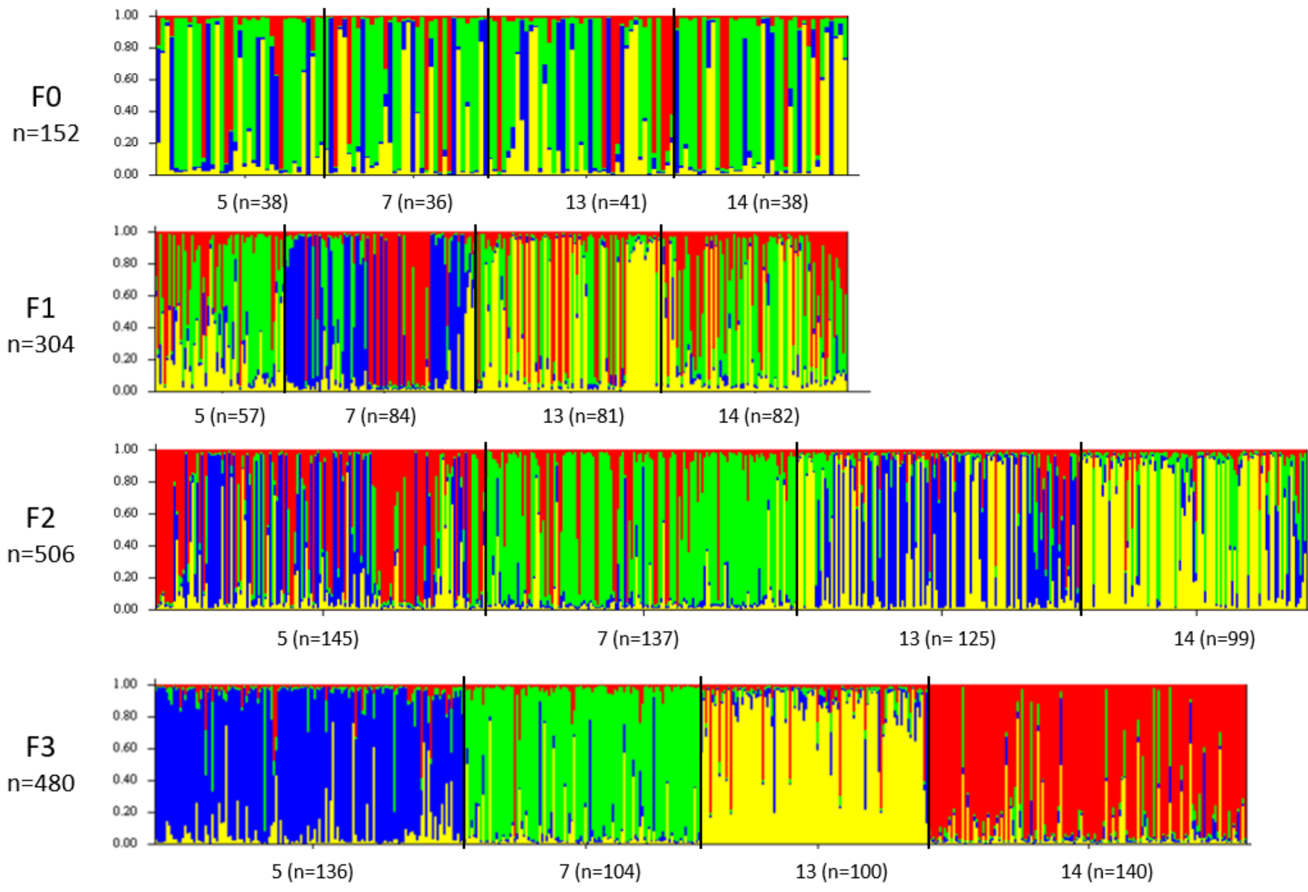

FIGURE 4 STRUCTURE analysis for F0–F3 individuals of all enclosures. As four separate enclosures (5, 7, 13 and 14) were used for this experiment, we showed STRUCTURE results for K = 4. Sample size is given for each STRUCTURE plot underneath the corresponding generation. Further, sample size per enclosure is given after enclosures numbers. Individuals are sorted according to their enclosures.

DISCUSSION

HQ food induced a generally faster POL with increasingly higher fecundity rates and reduced generation times. HQ animals developed a less proactive stress-coping style across generations. Life history and behavioural characteristics co-varied depending on the food quality. The differences between the populations living under different food qualities did not emerge due to neutral genetic differentiation between populations. This conclusion is bolstered by transcriptomic data indicating that common metabolic pathway adjusted causing the

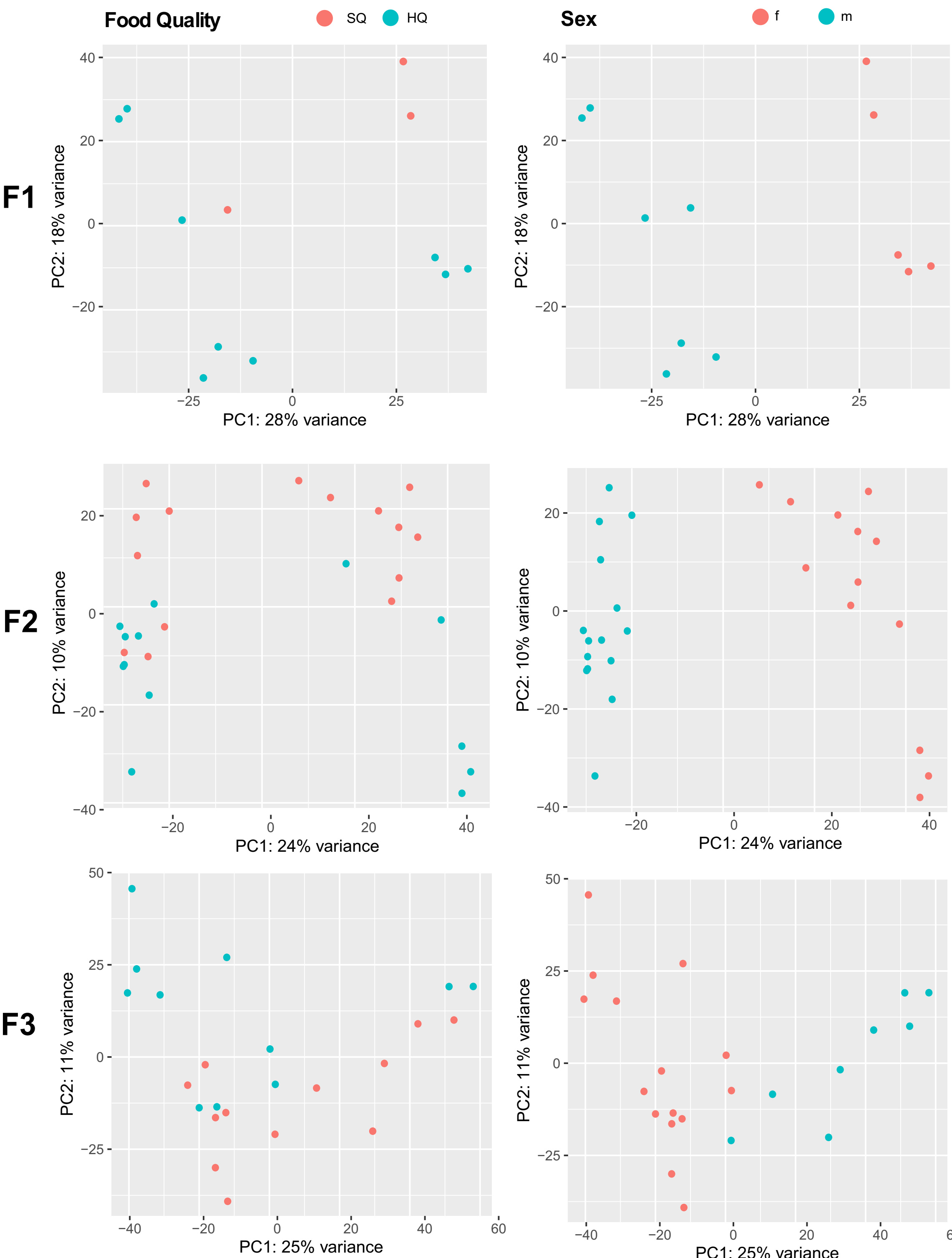

FIGURE 5 Principal component analysis of transcriptomic data for liver samples. Left: Labelled according to food treatment separately for each generation and right: According to sex separately for each generation.

phenotypic differences. Furthermore, constant levels of heterozygosities indicate no influence of inbreeding and R_{ST} indicate a differentiation comparable to levels observed in natural wild mouse populations (Linnenbrink et al., 2013).

Does HQ food induce a faster POL and corresponding changes in personality?

Fecundity rates and generation times start diverging from the F1 generation onwards with increasing

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magnitude in each subsequent generation. In the open field, HQ individuals covered considerably less distance than SQ individuals, again with increasing differentiation across the generations. Across treatments and generations, we found several between-individual correlations of life history and behavioural traits, albeit not in the predicted direction (Réale et al., 2010). Understanding the origin and the evolution of such syndromes is a current focus of organismal biology (Agrawal, 2020). Nevertheless, empirical evidence supporting the POLS hypothesis remains ambiguous (Agrawal, 2020; Dammhahn et al., 2018).

One factor potentially contributing to the ambiguity is the ecological relevance of behavioural tests used (Carter et al., 2013). In mice, coping with an open field in a reactive (characterised by prolonged freezing behaviour and little movement) versus proactive (active exploration of the arena) way is a strong predictor of risk-taking, predicting large-scale exploration and dispersal events (Krackow, 2003; Krebs et al., 2019). We also planned our whole experiment as ecologically relevant as possible but with full control over reproductive events and generations which would not have been possible under completely natural conditions. The design of the semi-natural enclosures was carefully validated before the main experiment so that the observed population growth, survival and offspring recruitment were well in the range of naturally observed commensal house mouse populations despite the absence of several potentially important natural selective pressures such as parasites, diseases or predators (Gómez et al., 2008, Pockock & Searle 2004) (see Supplementary materials S1–S3). We saw a strong effect on behaviour when shifting from cage housing to semi-natural living and vice versa (Supplementary material S8) with animals being kept in cages (F2) or having grown up in cages (F0) running around more in the Open Field. Such effects call for a careful interpretation of results derived from standard laboratory settings.

While many studies in the past tested for POLS predictions without teasing apart within from among-individual variation (Dammhahn et al., 2018), the POLS framework specifically predicts associations of life history with behaviour at the among-individual level. We found such consistent between-individual covariation with proactive individuals also having higher generation time. Interestingly, this association was even stronger in HQ animals. While we found no emerging treatment difference on exploration, the number of exploration trips and the time spent exploring were associated with generation time as well, at least for the HQ animals. The trait associations we found are in line with the asset-protection theory stating that animals with a high residual reproductive value would have more to lose if injured or killed and should therefore take fewer risks than animals with a low residual reproductive value (Clark, 1994; Wolf et al., 2007).

One potentially important factor hypothesised to contribute to ambiguous findings regarding POLS, are environmental conditions (Hämäläinen et al., 2021; Montiglio et al., 2018). Links between personality and life history may only emerge under specific socio-ecological conditions or may be masked by others. The relationship between personality, survival and reproduction in Eurasian red squirrels (*Sciurus vulgaris*) for example, was found to depend on the habitat (Santicchia 2018). Our study is one of the first to show that an environmental change induces changes in correlations between life history and personality within only a few generations. Although both behaviours showed changes in correlations to life history, only the open field behaviour also showed a change in population mean. Possibly, other factors than food quality contribute to the different patterns across traits. One striking aspect are sex differences in the novel environment but not in the Open Field test. Sex-specific POLS have been predicted because of different investment strategies into reproduction (Immonen et al., 2018) and were found to be especially pronounced in polygynous systems such as mice (Tarka et al., 2018). Voluntary risk-taking and exploration might be more important for allocation strategies closely related to other life-history trade-offs such as the offspring quality versus quantity trade-off. Theoretical predictions suggest two reproductive strategies, whereby fast-lived and risk-taking individuals should emphasise offspring quantity while risk-averse, slow individuals should favour offspring quality (Alvergne et al., 2010). Under HQ conditions, mothers usually weaned more offspring per litter while SQ mothers often reduced the litter size postnatally. This suggests an adjustment towards quantity over quality in the HQ treatment.

Our results demonstrate a general importance of the nutritional environment on life history, behaviour and the covariation between them as already suggested by Han and Dingemanse (2017). In line with a recent meta-analysis, we showed that high risk-taking behaviour is promoted by poorer nutritional conditions (Moiron et al., 2020) albeit only in a forced situation, not when animals could choose to take risks. Other factors such as sex and/ or reproductive status of animals might have a stronger effect on individual decisions in a voluntary situation. Furthermore, we show for the first time that an environmental change influenced traits on different time-scales with some traits starting to diverge already in the F1 generation while others only showed a statistical difference in F2 or F3. Possibly, such difference in time-scales are brought about by the interplay of developmental mechanisms interacting with environmental cues (Trillmich et al., 2018). Several personality traits for example are strongly influenced during early life with only limited plasticity later, thus, responses to environmental change (and/ or internal state) may be delayed by one generation (Trillmich et al., 2018). Studies investigating the effects of the environment only within one

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generation might thus fail to reveal important patterns and might thus further contribute to equivocal reports about POLS in the literature.

What are the underlying mechanisms of phenotypic adaptations?

An analysis of microsatellite allele distributions confirmed a similar spread of genotypes across all four enclosures in the founding generation. Across generations, the enclosures started to diverge. In the F3 generation, STRUCTURE analysis suggested four separate enclosure populations, indicating that while the 'populations' of similar food quality drifted apart genetically, they showed similar phenotypic responses. Importantly, there was no difference in gene expression profiles with enclosure identity. Still, functional genetic changes according to different food qualities might be involved in the adaptation process. However, genetic adaptation to a certain food quality would need to be incredible strong to be identified within three generations, and, in addition, would have happened in two populations in parallel, which both is highly unlikely.

Observing parallel adjustments of life history and behaviour within few generations despite genetic differentiation among enclosures suggests a strong influence of plasticity as the mechanism of fast adaptation to novel environments. Parental and grand-parental effects are increasingly recognised as drivers of fast adjustments (O'Dea et al., 2016; Snell-Rood et al., 2015). Evidence accumulates that plasticity plays an important role for evolutionary processes (Danchin, 2013; Ledón-Rettig, 2013) and often precedes changes in gene frequency (the 'plasticity first hypothesis', [Levis & Pfennig, 2016, Perry et al., 2018]). Long-term or even trans-generationally stable phenotypic adjustments, that is, irreversible or developmental plasticity, is thought to predict the future state of the environment through environmental cues (predictive adaptive response hypothesis [Bateson et al., 2014]). Plastic responses involve environment-specific gene expression (Lafuente & Beldade, 2019). Accordingly, we found differential gene expression according to food treatment in many genes associated with metabolic processes. Stable individual differences in metabolism are related to several behaviours, especially those that require high energetic output (Careau et al., 2008). Metabolic rate is thought to be a key driver for a wide range of biological processes (Pettersen et al., 2018) and has recently been shown to be positively related to fitness traits (Arnold et al., 2021). Our results thus support a key role of metabolism-driving adaptations, including life history and behaviours. Thus, our study is one of the first to provide evidence at the molecular level for metabolic processes inducing observable phenotypic changes.

In contrast to processes governed mainly by the liver, the number of genes showing differences in the hippocampus was limited. Earlier studies on laboratory rodents indicated correlations between hippocampal gene expression and behaviour (e.g. Weaver et al., 2006), however, our results under semi-natural conditions somewhat challenges the broader ecological relevance of such gene-expression patterns found in an artificial laboratory environment.

Interestingly, we found a difference in liver, but not hippocampal gene expression between the sexes. Given the strong sex differences in life history, we conclude that some sex-specific transcriptional plasticity is involved in the metabolic adjustment to the HQ food. Sex-specific gene expression occurs in many animal genomes (Connallon & Clark, 2010). Reproductive optima and longevity often differ between sexes (Fairbairn et al. 2007, Maklakov et al., 2008) and especially metabolism-fitness components can be sex-dependent because males and females often differ in energetic requirements (Boratyński et al., 2018), which may explain why fitness traits diverge on different time scales between males and females in our study.

Outlook

In our experiment, wild mice adapted their life history and behaviours to a change in food quality within three generations, causing a change in POLS structure. Interestingly, traits changed on different time scales (life history first, followed by behaviour) and changed differently between males and females. POLS theory predicts patterns of life history- behaviour covariation due to genetic correlations or trait integration via developmental (i.e. irreversible) plasticity (Dammhahn et al., 2018). Our data suggest a strong influence of transgenerational effects as one aspect of developmental plasticity. Despite much research, this area has remained largely unexplored so far and thus may offer new insight on the existence and maintenance of POLS. A promising route to understand patterns of POLS emergence brought about by plasticity across species is to better understand the proximate mechanisms including characterising gene-expression – behaviour and life history relationships in more detail.

AUTHOR CONTRIBUTIONS

NP conducted transcriptome and life history analyses. ML was responsible for analysis of microsatellite data, MJ and AG run and analysed all experiments with mice and AG conceived the study design. NP, ML and AG wrote the manuscript.

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for running thousands of microsatellite analyses. Furthermore, we would like to thank Diethard Tautz for constructive suggestions and discussions on the experiment. Open Access funding enabled and organized by Projekt DEAL.

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.

PEER REVIEW

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OPEN RESEARCH BADGES

This article has earned an Open Data badge for making publicly available the digitally-shareable data necessary to reproduce the reported results. The data is available at: https://doi.org/10.5061/dryad.fxpnvx0w4.

DATA AVAILABILITY STATEMENT

The raw data have been deposited at Dryad under: doi:10.5061/dryad.fxpnvx0w4.

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