Supplementary Information

Epigenetic regulation of the circadian gene *Perl* in the hippocampus contributes to agerelated changes in memory and synaptic plasticity

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Supplementary Figure 1. Genetic deletion or activity-specific disruption of HDAC3 in the dorsal hippocampus of aging mice. (a) Representative immunofluorescence images of HDAC3 (green) expression in HDAC3+/+ and HDAC3flox/flox mice injected with AAV2.1-CaMKII-Cre. Cell bodies were counterstained with a fluorescent Nissl stain (NeuroTrace, red). Right: mean intensity of HDAC3 immunofluorescence sampled from CA1 (normalized to background). HDAC3 expression was significantly reduced in HDAC3^{flox/flox} mice compared to HDAC3^{+/+} controls (t(30)=8.45, ***p<0.0001, n=14(5F), 18(6F)). (b) Representative immunfluorescence images of V5 (green) expression in wildtype mice injected with AAV-EV (Empty Vector control virus, top) or AAV2.1-CMV-HDAC3(Y298H)-V5 (bottom) counterstained with NeuroTrace (red). The V5 epitope tag added to HDAC3(Y298H)-V5 allowed us to selectively detect the HDAC3(Y298H)-v5 mutant without picking up endogenous HDAC3. Right: Mean intensity of V5 immunofluorescence (normalized to background). V5 expression was significantly higher in mice injected with AAV-HDAC3(Y298H)-V5 compared to AAV-EV controls (t(17)=6.33, p<0.0001, n=9,10, all male). (c) Experimental procedure. (d) HDAC3 mRNA expression in the dorsal hippocampus. HDAC3^{+/+} (gray bars) or HDAC3^{flox/flox} (blue bars) mice infused with AAV-Cre were sacrificed at rest (homecage) or 60m after OLM (OLM). HDAC3 mRNA expression was significantly reduced in HDAC3^{flox/flox} animals compared to HDAC3^{+/+} animals regardless of whether they received OLM training (Genotype group difference only, F(1,24) = 132.1, ***p < 0.0001, n = 6(2F), 6(3F), 8(5F), 8(5F)). Data are presented as mean ±SEM; Black circles, males, gray squares, females.



Supplementary Figure 2. All groups show normal short-term memory, movement, and anxiety. (a) Experimental schematic testing short-term memory. Two weeks after AAV-CaMKII-Cre infusion into the DH, 18-month-old HDAC3^{+/+} and HDAC3^{flox/flox} mice were trained in OLM and tested 60m later. **(b)** Both groups showed intact memory for OLM when tested 60m after training (Two-way ANOVA: Main effect of Session (F(1,11)=28.99, p<0.001), Sidak's *post hoc* tests, *p<0.05, **p<0.01, no significant differences observed between groups at either training or test, n=5,8; all male). **(c)** Both groups also showed similar levels of total exploration ($t_{(11)}$ =0.68, p=0.511). **(d)** A subset of animals from Figure 1B were tested in the elevated plus maze. Both groups showed similar levels of anxiety, as indicated by the percentage of time spent in the closed and open arms (Effect of Arm only, $F_{(1,9)}$ =38.47, ***p<0.001, n= 6(4F), 5(1F)). **(e)** Total distance traveled during each day of OLM habituation for mice in Figure 1B. No group differences. **(f)** Total distance traveled during ORM habituation for mice in Figure 1G. No group differences were observed and individual comparisons between groups each day revealed no significant differences. Data are presented as mean ±SEM. Black circles, males; gray circles, females.



Supplementary Figure 3. RNA sequencing quality controls and characterization of individual genes. (a) Mean PHRED quality scores for each animal in the six different groups: 18-m.o. HDAC3^{flox/flox} homecage (H3F-HC), 18-m.o. HDAC3^{flox/flox} behavior (H3F-BV), 18-m.o. wildtype homecage (OWT-HC), 18-m.o. wildtype behavior (OWT-BV), 3-m.o. wildtype homecage (YWT-HC), and 3-m.o. wildtype behavior (YWT-BV). (b) Percentage of short-reads uniquely aligned to the reference genome (blue bars) and transcriptome (red bars) and percentage of annotated genes covered by the sequencing reads (yellow bars) for each of the six groups. **(c-f)** Characterization of individual genes in 18-m.o. wildtype and HDAC3^{flox/flox} mice after learning, from Figure 3. **(c)** *Arc* mRNA expression (Effect of training only ($F_{(1,25)}$ =17.31, p = 0.0003), Sidak's *post hoc* tests, *p<0.05, *p<0.01, n=6(2F),7 (3F),8(5F), 8(5F)). **(d)** *cFos* mRNA expression (No significant effects, n=6(2F), 7(3F), 7(4F), 7(5F)). **(e)** H4K8Ac occupancy at the *Arc* promoter (No significant effects, n = 7(5F), 11(4F), 11(4F), 12(7F)). **(f)** H4K8Ac occupancy at the *cFos* promoter (No significant effects, n=9(5F), 11(4F), 13(6F), 11(6F)). Data are presented as mean ±SEM. Black circles, males; gray circles, females.



Supplementary Figure 4. Deletion of HDAC3 in the DH does not affect circadian rhythm of young or old mice. (a) Experimental procedure. (b-e) Representative actograms depicting circadian behavior for each group. Red dotted line indicates the switch from LD to DD. (b) Young HDAC3^{+/+} actogram. (c) Old HDAC3^{+/+} actogram. (d) Young HDAC3^{flox/flox} actogram. (e) Old HDAC3^{flox/flox} actogram. (f) HDAC3 deletion in DH did not affect free-running tau in either young or old mice (no significant effects, n=8,8,7,8; all males). Data are presented as mean ±SEM.



Supplementary Figure 5. Full-length western blot illustrating siRNA-mediated reduction in PER1. Proteins were identified with an anti-Per1 antibody (left, 30-minute exposure) followed by stripping and an anti-GAPDH antibody (right, 10-second exposure). Dotted boxes indicate the portion of the figure shown in Figure 4d.



Supplementary Figure 6. Per1-pLVX and Per1 CRISPR-SAM expression in the dorsal hippocampus of aging mice. (a) Example immunofluorescence images of V5 (green) expression in mice injected with either pLVX-EV (left) or pLVX-v5Per1 (right). Cell bodies were counterstained with a fluorescent Nissl stain (NeuroTrace, red). (b) *Per2* mRNA was significantly increased 24h after transfection of pLVX-v5Per1 in HT22 cells compared to cells transfected with pLVX-EV (Two-way ANOVA, significant Group x Time interaction (F(1,8)=21.28, p<0.01), Sidak's *post hoc* tests, ***p<0.001, n=3,3,3,3). (c) *Hes7* mRNA was unchanged 24h or 48h after pLVX-v5Per1 transfection (Two-way ANOVA, no significant main effect or interaction, n=3,3,3,3). (d) Example immunofluorescence images of GFP (green) expression in mice injected with the CRISPR-SAM system either with sgRNA lacking the *Per1* target sequence (Ctrl sgRNA, left) or with the Per1 guide RNA (Per1 sgRNA, right). Both groups show expression of GFP, a component of the dCas9-VP64-GFP plasmid injected in both groups. (e) *Per2* mRNA was unchanged by CRISPR-SAM transfection (Two-way ANOVA, no significant main effect or interaction, n=3,3,3,3). (f) *Hes7* mRNA was also unchanged by *Per1* CRISPR-SAM transfection (Two-way ANOVA, no significant main effect or interaction, n=3,3,3,3). (b) *Per2* mRNA was also unchanged by *Per1* CRISPR-SAM transfection (Two-way ANOVA, no significant main effect or interaction, n=3,3,3,3). (f) *Hes7* mRNA was also unchanged by *Per1* CRISPR-SAM transfection (Two-way ANOVA, no significant main effect or interaction, n=3,3,3,3). (f) *Hes7* mRNA was also unchanged by *Per1* CRISPR-SAM transfection (Two-way ANOVA, no significant main effect or interaction, n=3,3,3,3). Data are presented as mean ±SEM.



Supplementary Figure 7. Transcript detection for Per1-overexpression plasmids using RNA-sequencing. (a) The pLVX-EV-mCherry sequence was only detected in hippocampal samples from animals injected with pLVX-EV-mCherry (b) The pLVX-v5Per1 sequence was only detected in the group injected with pLVX-v5Per1. (c) The dCas9-VP64-GFP sequence was detected in both CRISPR-SAM groups (EV sgRNA and Per1 sgRNA) but not in either pLVX group. (d) The EV sgRNA sequence was only detected in the CRISPR-SAM group injected with EV sgRNA. (e) The Per1 sgRNA sequence was only detected in the CRISPR-SAM group injected with Per1 sgRNA. n=3/group. Ctrl = control virus (EV or ctrl sgRNA); Per1 = Per1 OE virus (pLVX-v5Per1 or Per1 sgRNA). Data are presented as mean ±SEM. (f) Percent reads alignment rate for each of the four groups was similar. (g) Mean PHRED quality scores for each animal.



Supplementary Figure 8. All groups show normal movement during habituation. (A-E) Total distance traveled during each day of habituation for mice in figures 1D (a), 1I (b), 4E (c), 5C (d), and 5G (e). No group differences were observed and individual comparisons between groups each day revealed no significant differences. Data are presented as mean ±SEM.

| Increased expression | | | | | | | | |
|---|--|---|---|--|---|--|--|--|
| | Gene | Homecage Trained | | Fold Change | p-value | | | |
| | | (Mean) | (Mean) | (log) | - | | | |
| 1 | AF357426 | 0.123 | 1.062 | 0.939 | 9.75919E-12 | | | |
| 2 | A230065H16Rik | 0.651 | 3.996 | 3.345 | 1.28698E-10 | | | |
| 3 | Glp1r | 0.227 | 1.091 | 0.864 | 2.66057E-08 | | | |
| 4 | Prdm12 | 0.072 | 0.456 | 0.383 | 2.43083E-07 | | | |
| 5 | Gh | 0.007 | 0.350 | 0.343 | 2.02023E-06 | | | |
| 6 | Ano2 | 0.389 | 1.077 | 0.688 | 3.13868E-06 | | | |
| 7 | SIn | 0.668 | 2.403 | 1.734 | 3.40852E-06 | | | |
| 8 | lgfbpl1 | 1.597 | 2.459 | 0.862 | 5.53357E-06 | | | |
| 9 | Ctxn3 | 0.943 | 2.588 | 1.646 | 6.99663E-06 | | | |
| 10 | Ngb | 0.552 | 1.313 | 0.761 | 8.55593E-06 | | | |
| 11 | Magel2 | 0.141 | 0.418 | 0.277 | 2.82686E-05 | | | |
| 12 | Mir702 | 0.000 | 0.110 | 0.110 | 3.61675E-05 | | | |
| 13 | Isl1 | 0.018 | 0.239 | 0.221 | 5.03269E-05 | | | |
| 14 | C130060K24Rik | 0.051 | 0.230 | 0.179 | 7.6283E-05 | | | |
| 15 | Gpr88 | 0.762 | 2.072 | 1.310 | 0.000132281 | | | |
| 16 | Mir7009 | 0.000 | 0.158 | 0.158 | 0.000179688 | | | |
| 17 | Zic1 | 2.590 | 7.161 | 4.571 | 0.000236958 | | | |
| 18 | Sost | 0.056 | 0.253 | 0.197 | 0.000278343 | | | |
| 19 | C130074G19Rik | 5.293 | 8,409 | 3,116 | 0.000297396 | | | |
| 20 | DIx1 | 4.424 | 6.604 | 2.180 | 0.000537434 | | | |
| - | | | | | | | | |
| | | Decrease | ea express | sion | | | | |
| | Cono | Homecage | ed express | Fold Change | n voluo | | | |
| | Gene | Homecage (Mean) | ed express Trained (Mean) | Fold Change (log) | p-value | | | |
| 1 | Gene Mir804 | Homecage (Mean) 0.380 | d express Trained (Mean) 0.065 | Fold Change (log) -0.316 | p-value 4.79591E-08 | | | |
| 1 | Gene Mir804 DQ267100 | Decrease Homecage (Mean) 0.380 1.702 | rained (Mean) 0.065 0.561 | Fold Change (log) -0.316 -1.141 | p-value 4.79591E-08 5.03473E-06 | | | |
| 1 2 3 | Gene Mir804 DQ267100 Mir486 | Decrease Homecage (Mean) 0.380 1.702 0.312 | d express Trained (Mean) 0.065 0.561 0.058 | Fold Change (log) -0.316 -1.141 -0.254 | p-value 4.79591E-08 5.03473E-06 7.96871E-06 | | | |
| 1 2 3 4 | Gene Mir804 DQ267100 Mir486 Cpne7 | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 | Content Content <t< td=""><td>Fold Change (log) -0.316 -1.141 -0.254 -8.732</td><td>p-value 4.79591E-08 5.03473E-06 7.96871E-06 8.44389E-06</td></t<> | Fold Change (log) -0.316 -1.141 -0.254 -8.732 | p-value 4.79591E-08 5.03473E-06 7.96871E-06 8.44389E-06 | | | |
| 1 2 3 4 5 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 | A express Trained (Mean) 0.065 0.561 0.058 38.314 0.064 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 | p-value 4.79591E-08 5.03473E-06 7.96871E-06 8.44389E-06 1.00325E-05 | | | |
| 1 2 3 4 5 6 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 | A express Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.039 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-05 | | | |
| 1 2 3 4 5 6 7 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 | Content Content <t< td=""><td>Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.039 -0.029</td><td>p-value 4.79591E-08 5.03473E-06 7.96871E-06 8.44389E-06 1.00325E-05 2.98682E-05 0.000129378</td></t<> | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.039 -0.029 | p-value 4.79591E-08 5.03473E-06 7.96871E-06 8.44389E-06 1.00325E-05 2.98682E-05 0.000129378 | | | |
| 1 2 3 4 5 6 7 8 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 | A express Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 0.000 0.000 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.039 -0.029 -0.066 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.000159265 | | | |
| 1 2 3 4 5 6 7 8 9 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 1700020M21Rik | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 0.028 | A express Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 0.000 0.000 0.000 0.000 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.039 -0.029 -0.066 -0.028 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.0001592650.000168869 | | | |
| 1 2 3 4 5 6 7 8 9 10 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 1700020M21Rik Mir367 | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 0.028 0.039 | Additional expression Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 0.000 0.000 0.000 0.000 0.000 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.039 -0.029 -0.028 -0.039 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.0001592650.0001688690.000393218 | | | |
| 1 2 3 4 5 6 7 8 9 10 11 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 1700020M21Rik Mir367 Grp | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 0.028 0.039 8.839 | A express Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.039 -0.029 -0.066 -0.028 -0.039 -2.061 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.0001592650.0001688690.0003932180.000451035 | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 1700020M21Rik Mir367 Grp Eif3j1 | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 0.028 0.039 0.445 | Additional Additiona Additiona Additiona | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.039 -0.029 -0.066 -0.028 -0.039 -0.039 -0.0445 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.0001592650.0001688690.0004510350.001197766 | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 1700020M21Rik Mir367 Grp Eif3j1 Snord123 | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 0.028 0.039 8.839 0.445 | Additional expression Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.029 -0.066 -0.028 -0.039 -0.0445 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.0001592650.0001688690.0003932180.0001977660.001221741 | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 1700020M21Rik Mir367 Grp Eif3j1 Snord123 Hbq1a | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 0.028 0.039 0.445 0.136 | Additional expression Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.039 -0.029 -0.066 -0.039 -0.039 -0.0445 -0.136 -0.227 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.0001592650.0001688690.0003932180.0004510350.0012217410.001656455 | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 1700020M21Rik Mir367 Grp Eif3j1 Snord123 Hbq1a Mir202 | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 0.028 0.039 8.839 0.445 0.136 0.295 0.029 | Additional expression Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.039 -0.029 -0.066 -0.028 -0.039 -2.061 -0.445 -0.136 -0.227 -0.029 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.0001592650.0001688690.0003932180.0004510350.0011977660.0016564550.002539309 | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 1700020M21Rik Mir367 Grp Eif3j1 Snord123 Hbq1a Mir202 Nov | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 0.028 0.039 0.445 0.136 0.295 0.029 | Additional expression Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 30.697 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.029 -0.028 -0.039 -2.061 -0.445 -0.136 -0.227 -0.029 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.0001592650.0001688690.0003932180.0001977660.0012217410.0016564550.0025393090.002754578 | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 1700020M21Rik Mir367 Grp Eif3j1 Snord123 Hbq1a Mir202 Nov Snora34 | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 0.028 0.039 0.445 0.136 0.295 0.029 | Additional expression Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 30.697 0.725 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.029 -0.066 -0.028 -0.039 -0.136 -0.227 -0.029 -1.140 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.0001592650.0001688690.0003932180.0004510350.0011977660.0012217410.0016564550.0025393090.0027545780.002813874 | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 1700020M21Rik Mir367 Grp Eif3j1 Snord123 Hbq1a Mir202 Nov Snora34 Mir699n | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 0.028 0.039 8.839 0.445 0.136 0.295 0.029 37.795 1.884 0.090 | Additional expression Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 30.697 0.725 0.000 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.029 -0.066 -0.039 -0.039 -0.0445 -0.136 -0.227 -0.029 -1.160 -0.090 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.0001592650.0001688690.0003932180.0004510350.0012217410.0016564550.0025393090.0027545780.0028138740.003749518 | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 | Gene Mir804 DQ267100 Mir486 Cpne7 Mir1668 2310003N18Rik D16Ertd519e Mir698 1700020M21Rik Mir367 Grp Eif3j1 Snord123 Hbq1a Mir202 Nov Snora34 Mir6947 | Decrease Homecage (Mean) 0.380 1.702 0.312 47.046 0.447 0.039 0.029 0.066 0.028 0.039 0.445 0.136 0.295 0.029 37.795 1.884 0.090 0.080 | A express Trained (Mean) 0.065 0.561 0.058 38.314 0.064 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.725 0.000 0.014 | Fold Change (log) -0.316 -1.141 -0.254 -8.732 -0.383 -0.029 -0.028 -0.039 -0.039 -0.028 -0.136 -0.227 -0.029 -7.097 -1.160 -0.090 | p-value4.79591E-085.03473E-067.96871E-068.44389E-061.00325E-052.98682E-050.0001293780.0001592650.0001688690.0003932180.0004510350.0011977660.0012217410.0016564550.0025393090.0027545780.0037495180.004189413 | | | |

Supplementary Table 1

Genes with increased (top) or decreased (bottom) expression in young (3-m.o.) wildtype mice 60m after OLM training (trained) compared to baseline (homecage). The top 20 genes increased or decreased (based on *p*-value, homecage vs trained) are shown.

| Increased expression | | | | | | |
|--|---|---|---|---|---|--|
| | Cono | Homecage | Trained | Fold Change | n voluo | |
| | Gene | (Mean) | (Mean) | (log) | p-value | |
| 1 | Nr4a3 | 13.257 | 20.963 | 7.706 | 7.43057E-06 | |
| 2 | Ak4 | 6.212 | 9.271 | 3.059 | 8.98888E-05 | |
| 3 | Mir344d-2 | 0.000 | 0.249 | 0.249 | 0.000105067 | |
| 4 | Slit2 | 1.970 | 3.727 | 1.757 | 0.000166913 | |
| 5 | Tmem114 | 2.091 | 3.443 | 1.351 | 0.000181875 | |
| 6 | Mir7054 | 0.009 | 0.261 | 0.252 | 0.000278494 | |
| 7 | Sgk1 | 24.420 | 37.819 | 13.399 | 0.000317729 | |
| 8 | Mir7665 | 0.000 | 0.098 | 0.098 | 0.000451994 | |
| 9 | Mir7232 | 0.009 | 0.289 | 0.280 | 0.000463299 | |
| 10 | Gm11213 | 0.000 | 0.105 | 0.105 | 0.000771559 | |
| 11 | Sap18 | 1.153 | 2.875 | 1.722 | 0.000831838 | |
| 12 | Lpl | 10.900 | 15.275 | 4.374 | 0.001252228 | |
| 13 | Cldn22 | 2.520 | 4.334 | 1.814 | 0.001502037 | |
| 14 | Cox8b | 0.073 | 7.384 | 7.311 | 0.001810557 | |
| 15 | Pvrl3 | 6.285 | 9.501 | 3.216 | 0.001872061 | |
| 16 | Ccdc3 | 7.139 | 10.598 | 3.459 | 0.001908397 | |
| 17 | Coch | 1.422 | 4.054 | 2.632 | 0.001920303 | |
| 18 | Arl4d | 7.804 | 11.689 | 3.885 | 0.002276406 | |
| 19 | Mir7662 | 0.136 | 0.682 | 0.546 | 0.002427375 | |
| 20 | Pon1 | 0.000 | 0.509 | 0.509 | 0.002437193 | |
| | | Decrease | d expressio | n | | |
| | | Homecage | Trained | Fold Change | | |
| | Gene | (Mean) | (Mean) | (log) | p-value | |
| 1 | Cd72 | 31 100 | | | | |
| 0 | | 51.100 | 4.614 | -26.487 | 9.05719E-07 | |
| | Irf8 | 24.878 | 4.614 8.112 | -26.487 -16.766 | 9.05719E-07 1.64456E-06 | |
| ∠ 3 | Irf8 Il4ra | 24.878 10.307 | 4.614 8.112 2.185 | -26.487 -16.766 -8.122 | 9.05719E-07 1.64456E-06 1.74389E-06 | |
| ∠ 3 4 | Irf8 Il4ra Fcgr4 | 24.878 10.307 28.396 | 4.614 8.112 2.185 5.438 | -26.487 -16.766 -8.122 -22.958 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 | |
| 2 3 4 5 | Irf8 Il4ra Fcgr4 Themis2 | 24.878 10.307 28.396 9.935 | 4.614 8.112 2.185 5.438 2.454 | -26.487 -16.766 -8.122 -22.958 -7.481 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 | |
| 2 3 4 5 6 | Irf8 Il4ra Fcgr4 Themis2 Snord43 | 24.878 10.307 28.396 9.935 0.445 | 4.614 8.112 2.185 5.438 2.454 0.000 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 | |
| 2 3 4 5 6 7 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b | 24.878 10.307 28.396 9.935 0.445 1.652 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 | |
| 2 3 4 5 6 7 8 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.83063E-06 | |
| 2 3 4 5 6 7 8 9 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.83063E-06 9.22626E-06 | |
| 2 3 4 5 6 7 8 9 10 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b Scimp | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 4.059 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 0.557 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 -3.501 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.83063E-06 9.22626E-06 9.33703E-06 | |
| 2 3 4 5 6 7 8 9 10 11 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b Scimp Srgn | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 4.059 47.757 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 0.557 13.503 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 -3.501 -34.254 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.83063E-06 9.22626E-06 9.33703E-06 9.39187E-06 | |
| 2 3 4 5 6 7 8 9 10 11 12 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b Scimp Srgn Ubd | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 4.059 47.757 8.176 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 0.557 13.503 0.417 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 -3.501 -34.254 -7.760 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.83063E-06 9.22626E-06 9.33703E-06 9.39187E-06 | |
| 2 3 4 5 6 7 8 9 10 11 12 13 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b Scimp Srgn Ubd Pik3ap1 | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 4.059 47.757 8.176 16.416 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 0.557 13.503 0.417 6.053 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 -3.501 -34.254 -7.760 -10.363 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.83063E-06 9.22626E-06 9.33703E-06 9.39187E-06 1.10568E-05 | |
| 2 3 4 5 6 7 8 9 10 11 12 13 14 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b Scimp Srgn Ubd Pik3ap1 Tgm2 | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 4.059 47.757 8.176 16.416 25.834 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 0.557 13.503 0.417 6.053 7.395 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 -3.501 -34.254 -7.760 -10.363 -18.439 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.8063E-06 9.32626E-06 9.33703E-06 9.39187E-06 1.10568E-05 1.12324E-05 | |
| 2 3 4 5 6 7 8 9 10 11 12 13 14 15 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b Scimp Srgn Ubd Pik3ap1 Tgm2 Irf1 | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 4.059 47.757 8.176 16.416 25.834 36.175 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 0.557 13.503 0.417 6.053 7.395 11.774 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 -3.501 -34.254 -7.760 -10.363 -18.439 -24.400 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.83063E-06 9.22626E-06 9.33703E-06 9.39187E-06 1.10568E-05 1.12324E-05 1.13451E-05 | |
| 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b Scimp Srgn Ubd Pik3ap1 Tgm2 Irf1 Plac8 | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 4.059 47.757 8.176 16.416 25.834 36.175 53.527 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 0.557 13.503 0.417 6.053 7.395 11.774 7.757 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 -3.501 -34.254 -7.760 -10.363 -18.439 -24.400 -45.770 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.8063E-06 9.22626E-06 9.33703E-06 9.39187E-06 1.10568E-05 1.12324E-05 1.13451E-05 1.17837E-05 | |
| 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b Scimp Srgn Ubd Pik3ap1 Tgm2 Irf1 Plac8 Ccr5 | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 4.059 47.757 8.176 16.416 25.834 36.175 53.527 12.634 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 0.557 13.503 0.417 6.053 7.395 11.774 7.757 4.444 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 -3.501 -3.501 -3.501 -3.4.254 -7.760 -10.363 -18.439 -24.400 -45.770 -8.190 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.8063E-06 9.22626E-06 9.33703E-06 9.39187E-06 1.10568E-05 1.12324E-05 1.12324E-05 1.17837E-05 1.293E-05 | |
| 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b Scimp Srgn Ubd Pik3ap1 Tgm2 Irf1 Plac8 Ccr5 Batf2 | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 4.059 47.757 8.176 16.416 25.834 36.175 53.527 12.634 5.442 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 0.557 13.503 0.417 6.053 7.395 11.774 7.757 4.444 1.303 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 -3.501 -34.254 -7.760 -10.363 -18.439 -24.400 -45.770 -8.190 -4 139 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.8063E-06 9.22626E-06 9.33703E-06 9.39187E-06 1.10568E-05 1.12324E-05 1.12324E-05 1.17837E-05 1.293E-05 1.58681E-05 | |
| 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b Scimp Srgn Ubd Pik3ap1 Tgm2 Irf1 Plac8 Ccr5 Batf2 Dusp2 | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 4.059 47.757 8.176 16.416 25.834 36.175 53.527 12.634 5.442 4.600 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 0.557 13.503 0.417 6.053 7.395 11.774 7.757 4.444 1.303 1.214 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 -3.501 -34.254 -7.760 -10.363 -18.439 -24.400 -45.770 -8.190 -4.139 -3.386 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.8063E-06 9.22626E-06 9.33703E-06 9.39187E-06 1.10568E-05 1.12324E-05 1.12324E-05 1.17837E-05 1.293E-05 1.58681E-05 1.67166E-05 | |
| 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 | Irf8 Il4ra Fcgr4 Themis2 Snord43 Klrb1b Ptprc Fcgr2b Scimp Srgn Ubd Pik3ap1 Tgm2 Irf1 Plac8 Ccr5 Batf2 Dusp2 Fol2 | 24.878 10.307 28.396 9.935 0.445 1.652 16.345 29.445 4.059 47.757 8.176 16.416 25.834 36.175 53.527 12.634 5.442 4.600 20.901 | 4.614 8.112 2.185 5.438 2.454 0.000 0.115 4.806 8.814 0.557 13.503 0.417 6.053 7.395 11.774 7.757 4.444 1.303 1.214 5.857 | -26.487 -16.766 -8.122 -22.958 -7.481 -0.445 -1.537 -11.539 -20.631 -3.501 -3.501 -34.254 -7.760 -10.363 -18.439 -24.400 -45.770 -8.190 -4.139 -3.386 -15.044 | 9.05719E-07 1.64456E-06 1.74389E-06 2.21299E-06 2.38824E-06 2.52343E-06 7.80601E-06 7.8063E-06 9.22626E-06 9.33703E-06 9.39187E-06 1.10568E-05 1.12324E-05 1.12324E-05 1.12324E-05 1.12324E-05 1.293E-05 1.293E-05 1.67166E-05 1.68507E-05 | |

Supplementary Table 2 Genes with increased (top) or decreased (bottom) expression in old (18-m.o.) wildtype mice 60m after OLM training (trained) compared to baseline (homecage). The top 20 genes increased or decreased (based on *p*-value, homecage vs trained) are shown.

| Increased expression | | | | | | | | | | | |
|---|---|--|---|---|---|--|--|--|--|--|--|
| | Gene | Homecage | Trained | Fold Change | p-value | | | | | | |
| | | (Mean) | (Mean) | (log) | | | | | | | |
| 1 | Kcnc4 | 11.692 | 22.464 | 10.772 | 2.18475E-10 | | | | | | |
| 2 | Plk5 | 10.516 | 21.224 10.708 | | 3.79101E-07 | | | | | | |
| 3 | Arl4d | 8.143 | 12.922 4.780 | | 2.34263E-06 | | | | | | |
| 4 | Gabrd | 11.412 | 18.535 | 7.123 | 2.60145E-06 | | | | | | |
| 5 | Tnfrsf25 | 2.214 | 4.856 2.642 | | 3.03957E-06 | | | | | | |
| 6 | Mef2c | 21.021 | 32.112 | 11.091 | 3.14128E-06 | | | | | | |
| 7 | Sstr2 | 1.770 | 3.830 | 2.059 | 3.797E-06 | | | | | | |
| 8 | Gfra2 | 6.925 | 11.530 | 4.605 | 4.6487E-06 | | | | | | |
| 9 | Gsg1l | 7.038 | 11.922 | 4.884 | 4.9045E-06 | | | | | | |
| 10 | C1ql3 | 37.159 | 67.272 | 30.113 | 5.43282E-06 | | | | | | |
| 11 | Grm2 | 12.253 | 23.605 | 11.351 | 7.13077E-06 | | | | | | |
| 12 | Per1 | 13.384 | 19.212 | 5.828 | 8.99537E-06 | | | | | | |
| 13 | Stk32c | 32.308 | 48.977 | 16.669 | 1.62623E-05 | | | | | | |
| 14 | Tmem132a | 28.263 | 41.415 | 13.152 | 1.95184E-05 | | | | | | |
| 15 | Pak6 | 8.027 | 12.580 | 4.553 | 2.09096E-05 | | | | | | |
| 16 | Pcdh8 | 13.397 | 22.680 | 9.283 | 2.31057E-05 | | | | | | |
| 17 | Hlf | 21 758 | 32 986 | 11 228 | 2 37294E-05 | | | | | | |
| 18 | Trank1 | 23 176 | 35,030 | 11 854 | 2 75255E-05 | | | | | | |
| 10 | Nren | 10 592 | 18 779 | 8 187 | 3.05979E-05 | | | | | | |
| 20 | Nov1r | 6 282 | 10.773 | 4 562 | 3.08204E-05 | | | | | | |
| 20 | пруп | Decreas | ad express | ion | 20 NPy Ir 6.282 10.844 4.562 3.98204E-05 | | | | | | |
| | Gene Homecage | | | | | | | | | | |
| | Gene | Homecage | Trained | Fold Change | p-value | | | | | | |
| | Gene | Homecage (Mean) | Trained (Mean) | Fold Change | p-value | | | | | | |
| 1 | Gene Cd180 | Homecage (Mean) 22.518 | Trained (Mean) 6.494 | Fold Change (log) -16.024 | p-value | | | | | | |
| 1 | Gene Cd180 Cst7 | Homecage (Mean) 22.518 51.825 | Trained (Mean) 6.494 16.930 | Fold Change (log) -16.024 -34.895 | p-value 1.82021E-12 5.39092E-11 | | | | | | |
| 1 2 3 | Gene Cd180 Cst7 Cxcl13 | Homecage (Mean) 22.518 51.825 49.009 | Trained (Mean) 6.494 16.930 10.270 | Fold Change (log) -16.024 -34.895 -38.739 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 | | | | | | |
| 1 2 3 4 | Gene Cd180 Cst7 Cxcl13 B2m | Homecage (Mean) 22.518 51.825 49.009 2050.156 | Trained (Mean) 6.494 16.930 10.270 822.502 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 | | | | | | |
| 1 2 3 4 5 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2 469 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 | | | | | | |
| 1 2 3 4 5 6 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 | | | | | | |
| 1 2 3 4 5 6 7 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1 549 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 | | | | | | |
| 1 2 3 4 5 6 7 8 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 II18bp | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.23861E-09 | | | | | | |
| 1 2 3 4 5 6 7 8 9 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 Il18bp Barres2 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.03861E-09 4.6807E-09 | | | | | | |
| 1 2 3 4 5 6 7 8 9 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 II18bp Rarres2 H2-Oa | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 11.690 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 3.175 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 -8.515 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.23861E-09 4.6807E-09 5.08093E-09 | | | | | | |
| 1 2 3 4 5 6 7 8 9 10 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 Il18bp Rarres2 H2-Oa Psmb0 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 11.690 81.679 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 3.175 27.668 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 -8.515 54.011 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.23861E-09 4.6807E-09 5.08093E-09 5.723E-09 | | | | | | |
| 1 2 3 4 5 6 7 8 9 10 11 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 II18bp Rarres2 H2-Oa Psmb9 Cdf3 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 11.690 81.679 2.085 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 3.175 27.668 0.467 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 -8.515 -54.011 1 619 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.6807E-09 5.08093E-09 5.723E-09 6.91066E_09 | | | | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 Il18bp Rarres2 H2-Oa Psmb9 Gdf3 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 11.690 81.679 2.085 0.245 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 3.175 27.668 0.467 2.511 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 -8.515 -54.011 -1.619 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.6807E-09 5.08093E-09 5.723E-09 6.91066E-09 7.06282E_00 | | | | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 Il18bp Rarres2 H2-Oa Psmb9 Gdf3 Slamf8 Bin2 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 11.690 81.679 2.085 9.245 18.124 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 3.175 27.668 0.467 2.511 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 -8.515 -54.011 -1.619 -6.734 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.23861E-09 4.6807E-09 5.08093E-09 5.723E-09 6.91066E-09 7.06283E-09 7.21527E-00 | | | | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 II18bp Rarres2 H2-Oa Psmb9 Gdf3 Slamf8 Bin2 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 11.690 81.679 2.085 9.245 18.134 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 3.175 27.668 0.467 2.511 8.050 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 -8.515 -54.011 -1.619 -6.734 -10.084 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.23861E-09 4.6807E-09 5.723E-09 6.91066E-09 7.31527E-09 | | | | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 II18bp Rarres2 H2-Oa Psmb9 Gdf3 Slamf8 Bin2 H2-Q4 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 11.690 81.679 2.085 9.245 18.134 84.563 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 3.175 27.668 0.467 2.511 8.050 30.819 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 -8.515 -54.011 -1.619 -6.734 -10.084 -53.744 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.23861E-09 4.6807E-09 5.08093E-09 5.723E-09 6.91066E-09 7.36118E-09 | | | | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 Il18bp Rarres2 H2-Oa Psmb9 Gdf3 Slamf8 Bin2 H2-Q4 H2-DMb1 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 11.690 81.679 2.085 9.245 18.134 84.563 19.944 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 3.175 27.668 0.467 2.511 8.050 30.819 6.815 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 -8.515 -54.011 -1.619 -6.734 -10.084 -53.744 -13.128 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.23861E-09 4.6807E-09 5.08093E-09 5.723E-09 6.91066E-09 7.31527E-09 7.36118E-09 1.01291E-08 | | | | | | |
| $ \begin{array}{c} 1\\2\\3\\4\\5\\6\\7\\8\\9\\10\\11\\12\\13\\14\\15\\16\\17\\12\end{array} $ | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 Il18bp Rarres2 H2-Oa Psmb9 Gdf3 Slamf8 Bin2 H2-Q4 H2-L Q. 04 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 11.690 81.679 2.085 9.245 18.134 84.563 19.944 61.942 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 3.175 27.668 0.467 2.511 8.050 30.819 6.815 23.548 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 -8.515 -54.011 -1.619 -6.734 -10.084 -53.744 -13.128 -38.394 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.6807E-09 5.08093E-09 5.723E-09 6.91066E-09 7.36118E-09 1.01291E-08 1.19768E-08 | | | | | | |
| $ \begin{array}{c} 1\\2\\3\\4\\5\\6\\7\\8\\9\\10\\11\\12\\13\\14\\15\\16\\17\\18\\18\\18\\18\\18\\18\\18\\18\\18\\18\\18\\18\\18\\$ | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 Il18bp Rarres2 H2-Oa Psmb9 Gdf3 Slamf8 Bin2 H2-Q4 H2-DMb1 H2-L Gpr84 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 11.690 81.679 2.085 9.245 18.134 84.563 19.944 61.942 8.355 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 3.175 27.668 0.467 2.511 8.050 30.819 6.815 23.548 3.449 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 -8.515 -54.011 -1.619 -6.734 -10.084 -53.744 -13.128 -38.394 -4.906 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.23861E-09 4.6807E-09 5.08093E-09 5.723E-09 6.91066E-09 7.361327E-09 1.01291E-08 1.19768E-08 1.58238E-08 | | | | | | |
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 | Gene Cd180 Cst7 Cxcl13 B2m Cd36 H2-DMa Hcar2 Il18bp Rarres2 H2-Oa Psmb9 Gdf3 Slamf8 Bin2 H2-Q4 H2-L Gpr84 Lair1 | Homecage (Mean) 22.518 51.825 49.009 2050.156 2.865 36.402 6.767 33.348 43.032 11.690 81.679 2.085 9.245 18.134 84.563 19.944 61.942 8.355 12.122 | Trained (Mean) 6.494 16.930 10.270 822.502 0.396 13.806 1.549 8.993 15.889 3.175 27.668 0.467 2.511 8.050 30.819 6.815 23.548 3.449 5.280 | Fold Change (log) -16.024 -34.895 -38.739 -1227.654 -2.469 -22.596 -5.218 -24.355 -27.143 -8.515 -54.011 -1.619 -6.734 -10.084 -53.744 -13.128 -38.394 -4.906 -6.842 | p-value 1.82021E-12 5.39092E-11 1.20531E-10 4.097E-10 7.55399E-10 8.27047E-10 1.25317E-09 4.23861E-09 4.6807E-09 5.723E-09 6.91066E-09 7.36118E-09 1.01291E-08 1.19768E-08 1.83705E-08 | | | | | | |

Supplementary Table 3 Genes with increased (top) or decreased (bottom) expression in old (18-m.o.) HDAC3^{flox/flox} mice 60m after OLM training (trained) compared to baseline (homecage). The top 20 genes increased or decreased (based on *p*-value, homecage vs trained) are shown.

| Quantitative real-time PCR Primers and Probes | | | | | | |
|---|--------------------------------|-------------------------------|--------------------------------|----------------|--|--|
| Gene | Forward (5' to 3') | Reverse (5' to 3') | | Probe | | |
| GAPDH | ATGGTGAAGGTCGGTGTGA | AAT | CTCCACTTTGCCACTGC | TGGCGGTATTGG | | |
| Per1 | Per1 TGTCCGTCACCAGTCAGTGT CCAG | | GGCAGGTCTTCCATC | #22 (CTCCACCA) | | |
| Per2 | TCCGAGTATATCGTGAAGAACG | GAAGAACG CAGGATCTTCCCAGAAACCA | | #5 (TGTGGCTG) | | |
| Hes7 | GAGAGGACCAGGGACCAGA | TTCGCTCCCTCAAGTAGCC | | #78 (AGCTGGAG) | | |
| NR4A1 | AGCTTGGGTGTTGATGTTCC | TGATGTTCC GCCCTGCCTGGTAGAGT | | #93 (TCTGGTCC) | | |
| NR4A2 | TTGCAGAATATGAACATCGACA | GTTCCTTGAGCCCGTGTCT | | #2 (TTCTCCTG) | | |
| Arc | CGGGACCTGTACCAGACACT | GCCCACCACATACTGAATGA | | #63 (AGGAGGAG) | | |
| cFos | GGGGCAAAGTAGAGCAGCTA | AGCTCCCTCCTCCGATTC | | #46 (ATGGCTGC) | | |
| Hdac3 | Hdac3 TTCAACGTGGGTGATGACTG TTA | | GCTGTGTTGCTCCTTGC | #32 (CTGCTCCC) | | |
| Hdac3-V5 | TGGAGATTCTCGAGGGTAAGC | ATGCCACCCGTAGATCTGG | | #91 (CTCTCCTC) | | |
| ChIP Primers | | | | | | |
| Gene | Forward (5' to 3') | | Reverse (5' to 3') | | | |
| Per1 CRE | CAGCTGCCTCGCCCGCCTC | | CCCAAGCAGCCATTGCTCGC | | | |
| Per1 E-Box | CCCTCACTTCCCTTTCATTATTGACG | | TGCATAATGCCAGGCCCTGCCCCTCATTGG | | | |
| Per1 Prox | ACTGGGTGTAGCCAGCAGAT | | ACAGTGGAGGACGAAACAGG | | | |
| Arc | CGGGACCTGTACCAGACACT | | GCCCACCACATACTGAATGA | | | |
| cFos | TACGACCCCTTCAGGCATAC | | GTTTTAAAGGACGGCAGCAC | | | |

Supplementary Table 4 List of quantitative real-time PCR primers and probes (Roche Universal Probe Library) and ChIP primers (designed with Primer 3).