

Supplemental information

Table S1: Descriptive statistics of data from *Macro2* accelerated rotarod. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. *Macro2* used a factorial-ANOVA with repeated measures, hence the term Mouse name. x = not an exact F-test.

<i>Macro2</i> Rotarod	Latency to fall (s)		
	AGE	WT	<i>Macro2</i> KO
Female	3 months	196.3 \pm 13.2 N=20	201.1 \pm 11.3 N=17
Male		191.0 \pm 12.9 N=14	155.70 \pm 9.74 N=20
Female	13 months	207.6 \pm 12.7 N=16	193.0 \pm 12.5 N=16
Male		170.3 \pm 15.5 N=13	186.9 \pm 18.3 N=17
Genotype		F _(1,56) =0.97, p=0.327 x	
Sex		F _(1,56) =1.14, p=0.290 x	
Genotype*Sex		F _(1,56) =1.13, p=0.291 x	
Cohort		F _(1,56) =0.29, p=0.594	
Weight		F _(1,56) =18.49, p=0.006	
Weight*Sex		F _(1,56) =0.28, p=0.597	
Weight*Cohort		F _(1,56) =0.18, p=0.675	
Sex*Cohort		F _(1,56) =0.34, p=0.562	
Genotype*Cohort		F _(1,56) =1.11, p=0.296	
Mouse name		F _(1,56) =2.05, *p=0.003	

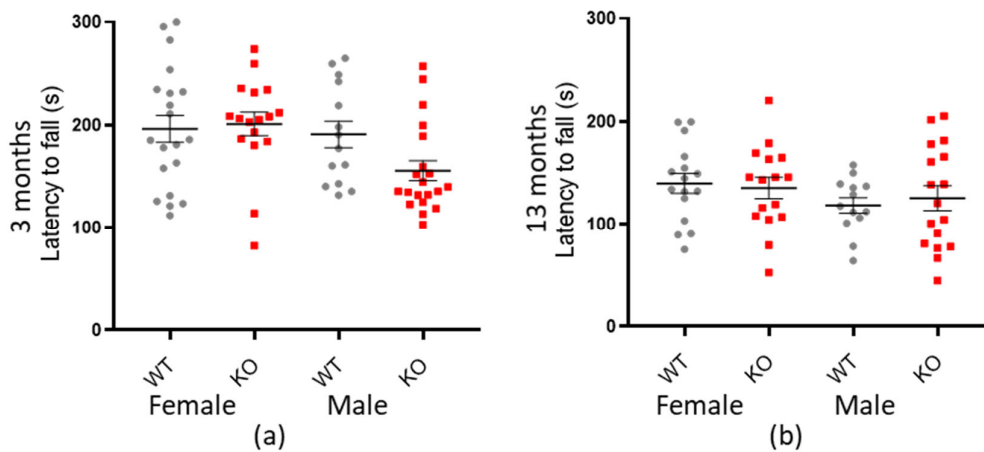


Figure S1: *Macro2* KO is not associated with reduced fall latency on the rotarod. Graphs show individual values dot plot, WT shown in grey circles and *Macro2* KO in red squares. Error bars are the SEM. Graphs are as follows a-b) *Macro2* 3 and 13 months.

Table S2: Descriptive statistics of central proportion from *Macro2* open field. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. *Macro2* used a factorial-ANOVA with repeated measures, hence the term Mouse name. x = not an exact F-test.

<i>Macro2</i> Open Field	Central %		
	AGE	WT	<i>Macro2</i> KO
Female	3 months	35.41 \pm 1.59 N=19	39.35 \pm 2.28 N=17
Male		39.61 \pm 1.36 N=14	43.40 \pm 1.80 N=20
Female	13 months	35.47 \pm 1.55 N=16	37.71 \pm 1.81 N=16
Male		40.11 \pm 1.19 N=13	39.73 \pm 1.74 N=17
Genotype		F _(1,55) =2.79, p=0.099 x	
Sex		F _(1,55) =0.23, p=0.635 x	
Genotype*Sex		F _(1,55) =0.11, p=0.737 x	
Cohort		F _(1,55) =0.46, p=0.501	
Weight		F _(1,55) =0.36, p=0.554	
Weight*Sex		F _(1,55) =0.38, p=0.538	
Weight*Cohort		F _(1,55) =0.60, p=0.441	
Sex*Cohort		F _(1,55) =0.01, p=0.917	
Genotype*Cohort		F _(1,55) =1.73, p=0.194	
Mouse name		F _(1,55) =1.68, *p=0.024	

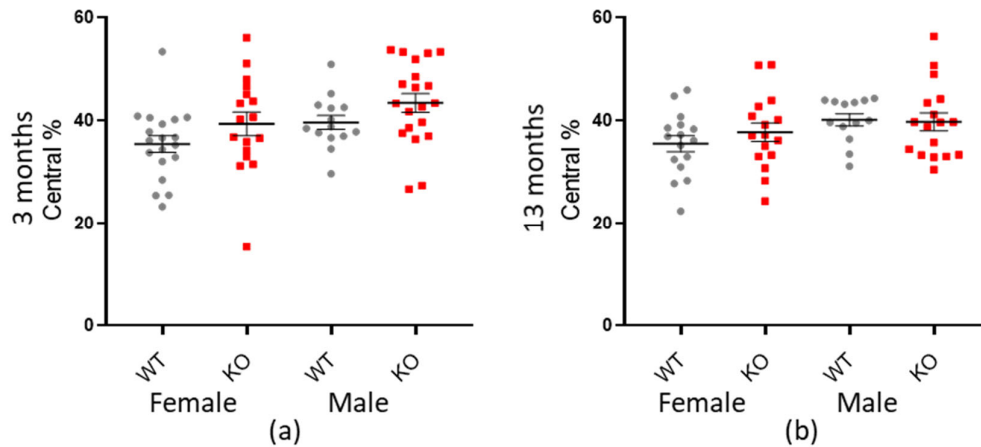


Figure S2: *Macro2* KO is not associated with anxiety in LMA Open Field. Graphs show individual values dot plot, WT shown in grey circles and *Macro2* KO in red squares. Error bars are the SEM. Graphs are as follows a-b) *Macro2* 3 and 13 months.

Table S3: Descriptive statistics of data from *MacroD1* LMA Open Field. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. *MacroD1* used a factorial-ANOVA.

<i>MacroD1</i> <i>Open Field</i>	<i>Total distance (beam breaks)</i>			<i>Central %</i>	
	AGE	WT	<i>MacroD1</i> KO	WT	<i>MacroD1</i> KO
Female	12 months	4704 \pm 321 N=13	4889 \pm 301 N=17	38.32 \pm 1.14 N=13	39.51 \pm 1.72 N=17
Male		4530 \pm 374 N=12	5161 \pm 483 N=12	36.46 \pm 1.49 N=12	37.74 \pm 1.57 N=12
Female	18 months	5660 \pm 251 N=17	5111 \pm 357 N=14	37.65 \pm 1.05 N=17	37.93 \pm 1.29 N=14
Male		4123 \pm 247 N=14	4074 \pm 295 N=12	40.52 \pm 1.54 N=14	41.50 \pm 1.94 N=12
Genotype		F _(1,100) =0.64, p=0.427		F _(1,100) =0.42, p=0.517	
Sex		F _(1,100) =0.05, p=0.826		F _(1,100) =1.16, p=0.284	
Genotype*Sex		F _(1,100) =0.00, p=0.981		F _(1,100) =0.34, p=0.561	
Cohort		F _(1,100) =0.55, p=0.461		F _(1,100) =0.95, p=0.332	
Weight		F _(1,100) =2.67, p=0.105		F _(1,100) =1.85, p=0.176	
Weight*Sex		F _(1,100) =0.01, p=0.921		F _(1,100) =0.64, p=0.426	
Weight*Cohort		F _(1,100) =0.41, p=0.524		F _(1,100) =0.34, p=0.561	
Weight*Genotype		F _(1,100) =0.63, p=0.430		F _(1,100) =0.53, p=0.467	
Sex*Cohort		F _(1,100) =2.14, p=0.146		F _(1,100) =0.92, p=0.340	
Genotype*Cohort		F _(1,100) =3.45, p=0.066		F _(1,100) =0.24, p=0.624	

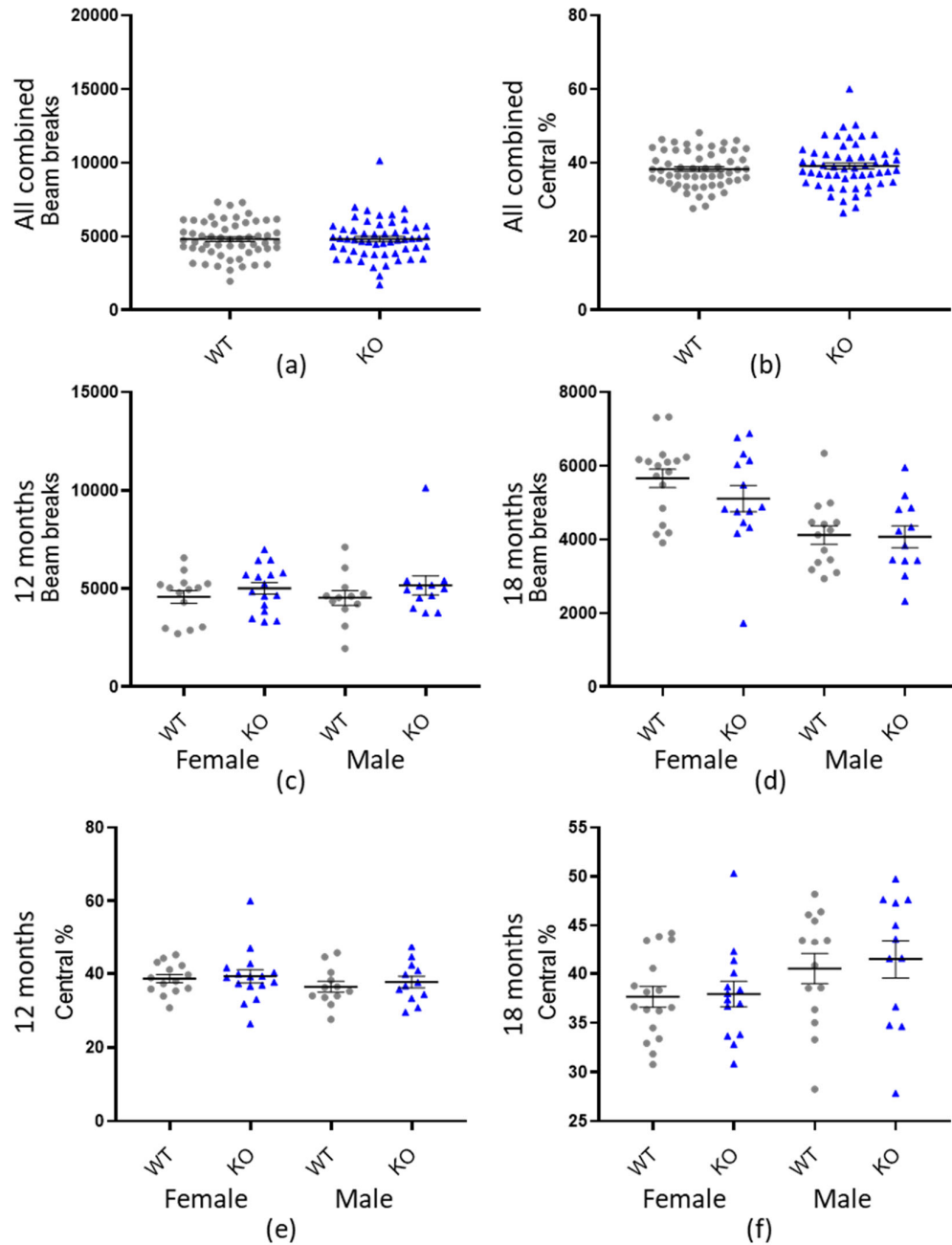


Figure S3: *Macrod1* KO is not associated with changes in locomotor activity or central proportion in LMA open field. Graphs show individual values dot plot, WT shown in grey circles and *Macrod1* KO in blue triangles. Error bars are the SEM. Graphs are as follows **a, c-d**) *Macrod1* LMA total beam breaks all combined, 12 and 18 months. **b, e-f**) *Macrod1* LMA central proportion (%) all combined, 12 and 18 months.

Table S4: Descriptive statistics of data from *Macro2* LMA Bright Field. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. *Macro2* used a factorial-ANOVA with repeated measures, hence the term Mouse name. x = not an exact F-test.

<i>Macro2</i> <i>Bright Field</i>	<i>Total distance (m)</i>			<i>Central (s)</i>	
	AGE	WT	<i>Macro2</i> KO	WT	<i>Macro2</i> KO
Female	3 months	26.06 \pm 1.00 N=20	28.44 \pm 1.48 N=17	8.18 \pm 1.23 N=20	6.153 \pm 0.802 N=17
Male		21.75 \pm 1.02 N=14	24.69 \pm 1.27 N=20	12.51 \pm 1.02 N=14	9.73 \pm 1.09 N=20
Female	13 months	31.75 \pm 2.00 N=15	32.77 \pm 2.64 N=16	5.595 \pm 0.869 N=15	9.37 \pm 1.22 N=16
Male		21.88 \pm 1.48 N=13	26.83 \pm 2.04 N=17	5.778 \pm 0.954 N=13	5.595 \pm 0.974 N=17
Genotype	F _(1,55) =3.33, p=0.072 x			F _(1,55) =0.00, p=0.955 x	
Sex	F _(1,55) =1.85, p=0.179 x			F _(1,55) =4.05, p=0.049 x	
Genotype*Sex	F _(1,55) =0.16, p=0.692 x			F _(1,55) =3.44, p=0.067 x	
Cohort	F _(1,55) =0.47, p=0.497			F _(1,55) =1.18, p=0.283	
Weight	F _(1,55) =0.03, p=0.870			F _(1,55) =0.00, p=0.955	
Weight*Sex	F _(1,55) =3.73, p=0.059			F _(1,55) =3.27, p=0.076	
Weight*Cohort	F _(1,55) =0.08, p=0.781			F _(1,55) =1.08, p=0.303	
Sex*Cohort	F _(1,55) =0.95, p=0.334			F _(1,55) =0.97, p=0.330	
Genotype*Cohort	F _(1,55) =0.04, p=0.847			F _(1,55) =7.71, *p=0.008	
Mouse name	F _(1,55) =2.10, *p=0.003			F _(1,55) =0.96, p=0.570	

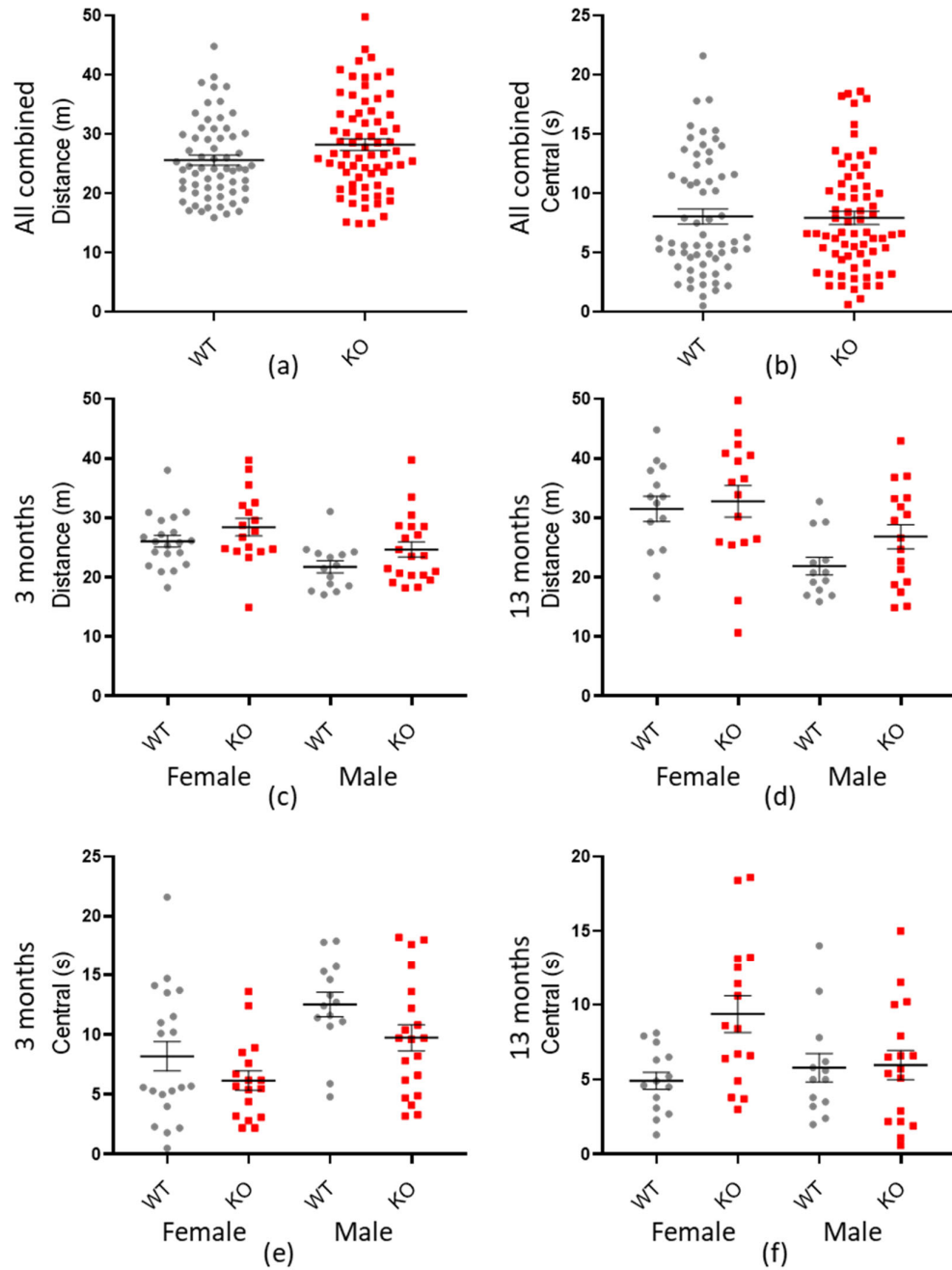


Figure S4: *Macrod2* KO is not associated with changes in locomotor activity or central proportion in LMA bright field. Graphs show individual values dot plot, WT shown in grey circles and *Macrod2* KO in red squares. Error bars are the SEM. Graphs are as follows **a, c-d**) total distance travelled (m) all combined, 3 and 13 months. **b, e-f**) central proportion (s) all combined, 3 and 13 months.

Table S5: Descriptive statistics of data from *MacroD1* LMA Bright Field. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. MacroD1 used a factorial-ANOVA.

<i>MacroD1</i> <i>Bright Field</i>	<i>Total distance (m)</i>			<i>Central (s)</i>	
	AGE	WT	<i>MacroD1</i> KO	WT	<i>MacroD1</i> KO
Female	12 months	17.81 \pm 1.29 N=10	18.62 \pm 1.26 N=17	5.680 \pm 0.915 N=10	4.724 \pm 0.730 N=17
Male		17.41 \pm 2.40 N=11	18.26 \pm 2.09 N=12	6.16 \pm 1.93 N=11	7.79 \pm 1.48 N=12
Female	18 months	19.96 \pm 1.26 N=17	23.46 \pm 1.60 N=14	3.765 \pm 0.589 N=17	4.314 \pm 0.584 N=14
Male		16.21 \pm 1.50 N=10	14.83 \pm 1.67 N=11	4.96 \pm 1.66 N=10	4.03 \pm 1.10 N=11
Genotype		F _(1,91) =0.34, p=0.559		F _(1,91) =1.57, p=0.214	
Sex		F _(1,91) =1.00, p=0.320		F _(1,91) =0.16, p=0.687	
Genotype*Sex		F _(1,91) =2.35, p=0.129		F _(1,91) =0.64, p=0.427	
Cohort		F _(1,91) =3.27, p=0.074		F _(1,91) =7.16, *p=0.009	
Weight		F _(1,91) =5.49, *p=0.021		F _(1,91) =4.02, *p=0.048	
Weight*Sex		F _(1,91) =1.10, p=0.297		F _(1,91) =0.01, p=0.914	
Weight*Cohort		F _(1,91) =4.19, *p=0.043		F _(1,91) =6.30, *p=0.014	
Weight*Genotype		F _(1,91) =0.40, p=0.529		F _(1,91) =1.51, p=0.222	
Sex*Cohort		F _(1,91) =6.78, *p=0.011		F _(1,91) =5.23, *p=0.024	
Genotype*Cohort		F _(1,91) =0.04, p=0.849		F _(1,91) =0.17, p=0.680	

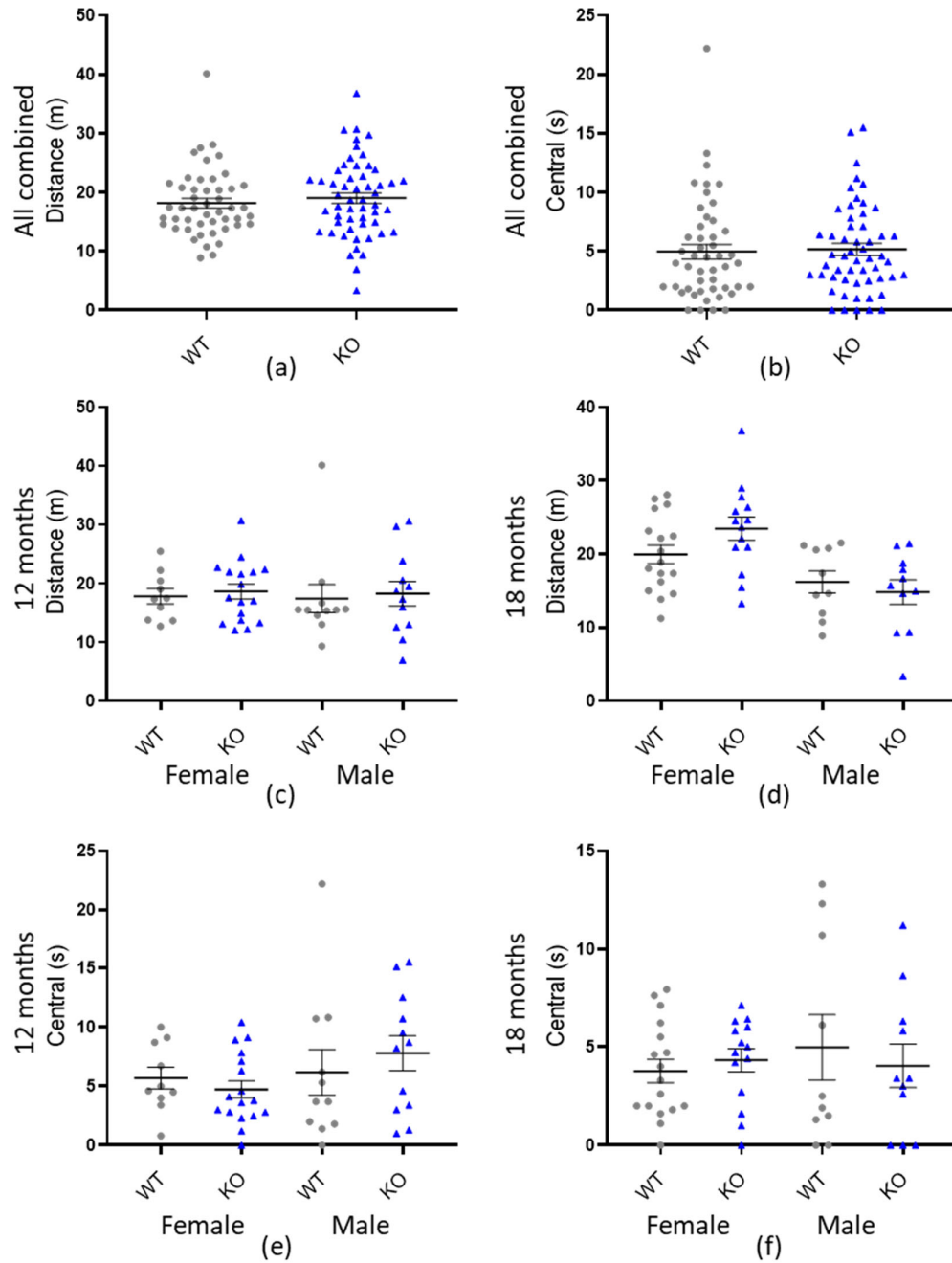


Figure S5: *MacroD1* KO is not associated with changes in locomotor activity or central proportion in LMA bright field. Graphs show individual values dot plot, WT shown in grey circles and *MacroD1* KO in blue triangles. Error bars are the SEM. Graphs are as follows **a, c-d** total distance travelled (m), all data combined, 12 and 18 months. **b, e-f** central proportion (s) all combined, 12 and 18 months.

Table S6: Descriptive statistics of preference ratio from *Macro2* Y-maze preference test. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. *Macro2* used a factorial-ANOVA with repeated measures, hence the term Mouse name. x = not an exact F-test.

<i>Macro2</i> Y-maze	Preference ratio		
	AGE	WT	<i>Macro2</i> KO
Female	3 months	0.7169 \pm 0.0359 N=17	0.6886 \pm 0.0376 N=15
Male		0.7628 \pm 0.0251 N=13	0.6594 \pm 0.0223 N=20
Female	13 months	0.6006 \pm 0.0528 N=16	0.6075 \pm 0.0527 N=16
Male		0.6127 \pm 0.0614 N=13	0.6107 \pm 0.0563 N=17
Genotype		F _(1,51) =0.41, p=0.522 x	
Sex		F _(1,51) =0.31, p=0.580 x	
Genotype*Sex		F _(1,51) =0.65, p=0.423 x	
Cohort		F _(1,51) =0.35, p=0.557	
Weight		F _(1,51) =0.07, p=0.787	
Weight*Sex		F _(1,51) =0.40, p=0.531	
Weight*Cohort		F _(1,51) =0.11, p=0.737	
Sex*Cohort		F _(1,51) =0.38, p=0.543	
Genotype*Cohort		F _(1,51) =1.09, p=0.301	
Mouse name		F _(1,51) =1.05, p=0.436	

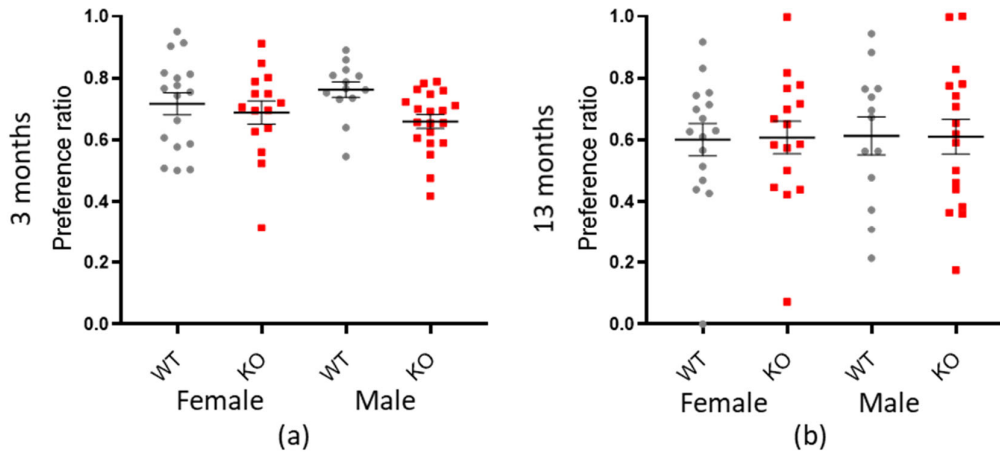


Figure S6: *Macro2* KO is not associated with changes in short term memory and attention. Graphs show individual values dot plot, WT shown in grey circles and *Macro2* KO in red squares. Error bars are the SEM. Graphs are as follows **a-b**) Preference ratio (from y-maze preference test) at 3 and 13 months.

Table S7: Descriptive statistics of data from *MacroD1* LMA Bright Field. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. *MacroD1* used a factorial-ANOVA.

<i>MacroD1</i> Y-maze	<i>Preference ratio</i>			<i>Distance travelled (m)</i>	
	AGE	WT	<i>MacroD1</i> KO	WT	<i>MacroD1</i> KO
Female	12 months	0.6980 \pm 0.0371 N=13	0.5785 \pm 0.0571 N=17	6.113 \pm 0.210 N=13	5.071 \pm 0.396 N=17
Male		0.6845 \pm 0.0432 N=18	0.6689 \pm 0.0507 N=13	4.953 \pm 0.335 N=18	5.209 \pm 0.299 N=13
Female	18 months	0.6703 \pm 0.0526 N=17	0.6294 \pm 0.0638 N=15	5.036 \pm 0.510 N=17	4.996 \pm 0.335 N=15
Male		0.5626 \pm 0.0858 N=13	0.4771 \pm 0.0662 N=12	3.573 \pm 0.413 N=13	3.677 \pm 0.440 N=12
Genotype		F _(1,107) =0.06, p=0.805		F _(1,107) =9.30, *p=0.003	
Sex		F _(1,107) =1.67, p=0.200		F _(1,107) =0.49, p=0.485	
Genotype*Sex		F _(1,107) =0.01, p=0.910		F _(1,107) =1.06, p=0.306	
Cohort		F _(1,107) =0.11, p=0.735		F _(1,107) =0.26, p=0.612	
Weight		F _(1,107) =0.53, p=0.468		F _(1,107) =2.50, p=0.117	
Weight*Sex		F _(1,107) =2.36, p=0.127		F _(1,107) =0.21, p=0.652	
Weight*Cohort		F _(1,107) =0.40, p=0.528		F _(1,107) =0.02, p=0.879	
Weight*Genotype		F _(1,107) =0.00, p=0.966		F _(1,107) =8.71, *p=0.004	
Sex*Cohort		F _(1,107) =0.07, p=0.790		F _(1,107) =1.87, p=0.175	
Genotype*Cohort		F _(1,107) =0.00, p=0.995		F _(1,107) =0.17, p=0.385	

Table S8: Descriptive statistics of distance travelled data from *MacroD1* distance travelled Y-maze preference test. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. Statistics was performed on all factors combined using a factorial-ANOVA. Whereas, separated by sex and age cohort comparisons used an ANCOVA (weight as a co-variable). The difference between the means is presented alongside a Cohen's d-score to demonstrate effect size.

<i>MacroD1</i> <i>Y-maze</i>	AGE	Total distance (m)				
		WT	<i>MacroD1</i> KO	Difference (m)	Cohen's d	<i>p-value</i>
Female	12 months	6.113 \pm 0.210 N=13	5.071 \pm 0.396 N=17	1.042	0.740	$F_{(1,27)}=4.31$, * $p=0.047$
Male		4.953 \pm 0.335 N=18	5.209 \pm 0.299 N=13	0.256	0.201	$F_{(1,28)}=0.03$, $p=0.869$
Female	18 months	5.036 \pm 0.510 N=17	4.996 \pm 0.335 N=15	0.04	0.023	$F_{(1,29)}=0.07$, $p=0.791$
Male		3.573 \pm 0.413 N=13	3.677 \pm 0.440 N=12	0.104	0.071	$F_{(1,22)}=0.00$, $p=0.958$
Genotype		$F_{(1,107)}=9.30$, * $p=0.003$				
Sex		$F_{(1,107)}=0.49$, $p=0.485$				
Genotype*Sex		$F_{(1,107)}=1.06$, $p=0.306$				
Cohort		$F_{(1,107)}=0.26$, $p=0.612$				
Weight		$F_{(1,107)}=2.50$, $p=0.117$				
Weight*Sex		$F_{(1,107)}=0.21$, $p=0.652$				
Weight*Cohort		$F_{(1,107)}=0.02$, $p=0.879$				
Weight*Genotype		$F_{(1,107)}=8.71$, * $p=0.004$				
Sex*Cohort		$F_{(1,107)}=1.87$, $p=0.175$				
Genotype*Cohort		$F_{(1,107)}=0.17$, $p=0.385$				

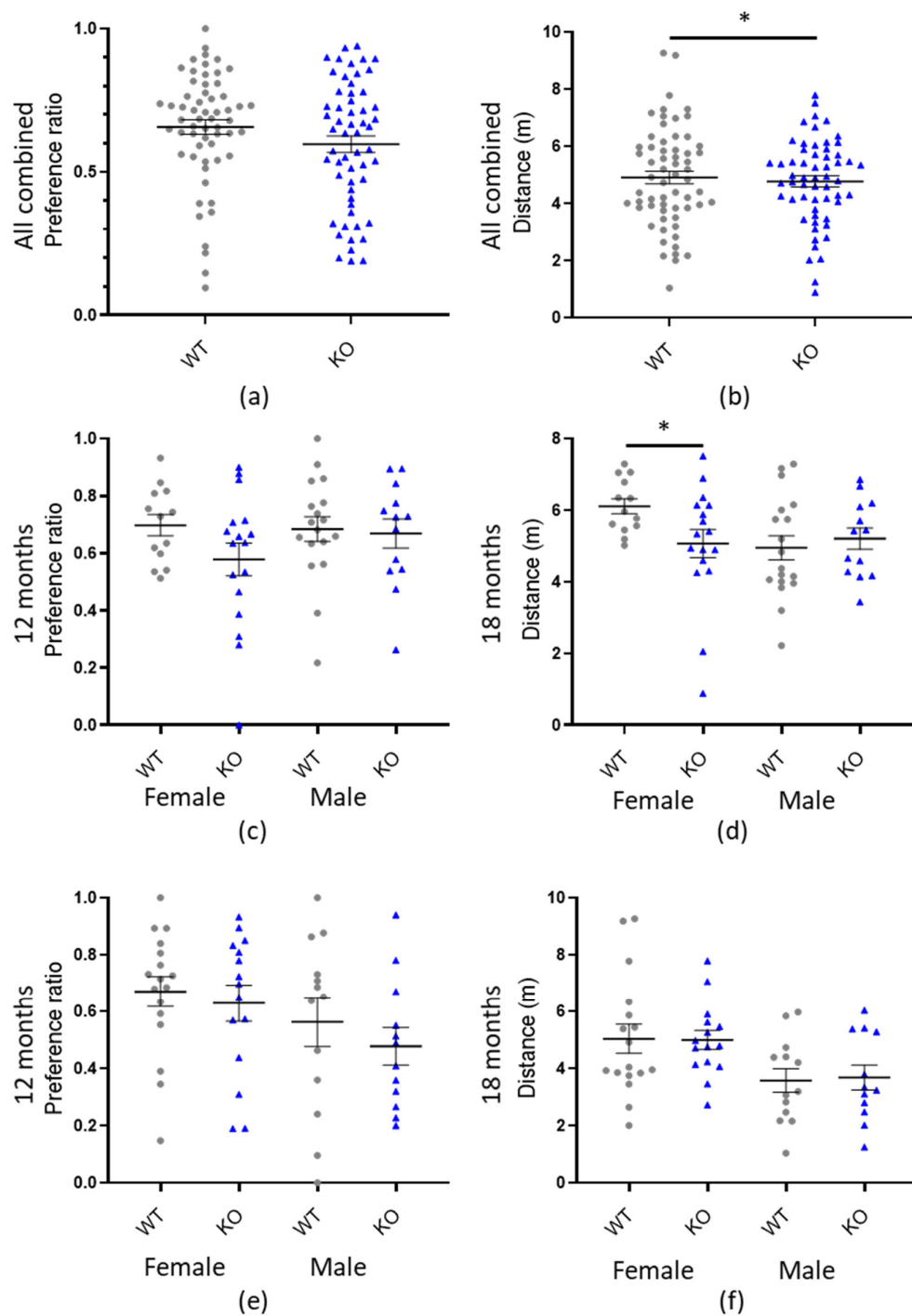


Figure S7: *Macrodl1* KO is not associated with changes in short term memory and attention. Results from the Y-maze preference test. Graphs show individual values dot plot, WT shown in grey circles and *Macrodl1* KO in blue triangles. Error bars are the SEM. Graphs are as follows **a, c-d**) preference ratio, all data combined, 12 and 18 months. **b, e-f**) total distance travelled (m) all combined, 12 and 18 months. Significant differences for

Macrodl distance travelled only **b)** overall $F_{(1,107)}=9.30$, $*p=0.003$ and **d)** 18 month old female mice $F_{(1,27)}=4.31$, $*p=0.047$.

Table S9: Descriptive statistics of SQRFore and hind paw intensity for *Macrodl* from the catwalk gait analysis. SQRFore = square root transformed. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. Statistics was performed on all factors combined using a factorial-ANOVA.

<i>Macrodl</i> Catwalk	SQRForepaw Intensity (arbitrary)			SQRForeHind Paw Intensity (arbitrary)	
	AGE	WT	<i>Macrodl</i> KO	WT	<i>Macrodl</i> KO
Female	12 months	8.915 \pm 0.117 N=13	8.8614 \pm 0.0731 N=15	8.860 \pm 0.137 N=13	8.7937 \pm 0.0778 N=15
Male		9.3944 \pm 0.0658 N=19	9.1560 \pm 0.0924 N=14	9.0620 \pm 0.0387 N=19	9.0842 \pm 0.0861 N=14
Female	18 months	9.168 \pm 0.133 N=16	8.9842 \pm 0.087 N=13	8.879 \pm 0.126 N=16	8.788 \pm 0.109 N=13
Male		9.7048 \pm 0.0676 N=12	9.4507 \pm 0.0874 N=12	9.1770 \pm 0.0709 N=12	9.090 \pm 0.115 N=12
Genotype		$F_{(1,103)}=0.03$, $p=0.859$		$F_{(1,103)}=0.64$, $p=0.426$	
Sex		$F_{(1,103)}=0.17$, $p=0.682$		$F_{(1,103)}=0.39$, $p=0.535$	
Genotype*Sex		$F_{(1,103)}=0.07$, $p=0.794$		$F_{(1,103)}=0.01$, $p=0.906$	
Cohort		$F_{(1,103)}=0.01$, $p=0.940$		$F_{(1,103)}=0.15$, $p=0.696$	
Weight		$F_{(1,103)}=13.15$, $*p < 0.001$		$F_{(1,103)}=0.02$, $p=0.902$	
Weight*Sex		$F_{(1,103)}=0.00$, $p=0.949$		$F_{(1,103)}=1.41$, $p=0.238$	
Weight*Cohort		$F_{(1,103)}=0.01$, $p=0.932$		$F_{(1,103)}=0.10$, $p=0.758$	
Weight*Genotype		$F_{(1,103)}=0.02$, $p=0.891$		$F_{(1,103)}=0.52$, $p=0.473$	
Sex*Cohort		$F_{(1,103)}=0.23$, $p=0.635$		$F_{(1,103)}=0.01$, $p=0.941$	
Genotype*Cohort		$F_{(1,103)}=0.11$, $p=0.739$		$F_{(1,103)}=0.65$, $p=0.424$	

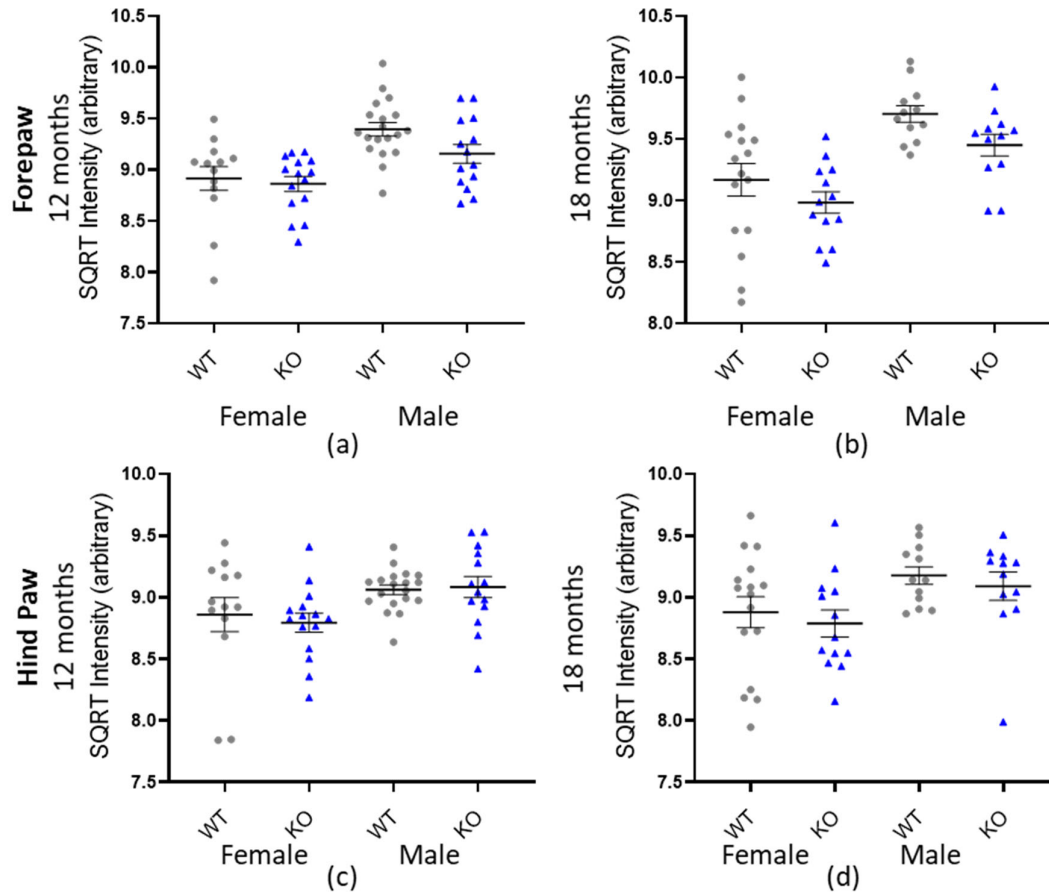


Figure S8: *Macrodl* KO is not associated with changes fore or hind paw foot pressure. Results from catwalk gait analysis. Graphs show individual values dot plot, WT shown in grey circles and *Macrodl* KO in blue triangles. SQRT = Square-root transformed. Error bars are the SEM. Graphs are as follows, **a-b)** forepaw intensity at 12 and 18 months, **c-d)** hind paw intensity at 12 and 18 months.

Table S10: Descriptive statistics of gait velocity and SQRT gait cadence for *Macrodl* from the catwalk gait analysis. SQRT = square root transformed. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. Statistics was performed on all factors combined using a factorial-ANOVA.

<i>Macrodl</i> Catwalk	Gait Velocity (cm/s)			SQRT Gait Cadence (steps/minute)	
	AGE	WT	<i>Macrodl</i> KO	WT	<i>Macrodl</i> KO
Female	12 months	23.13 \pm 1.07 N=13	25.15 \pm 1.92 N=15	3.9224 \pm 0.0905 N=13	3.955 \pm 0.102 N=15
Male		20.835 \pm 0.709 N=19	21.25 \pm 1.16 N=14	6.16 \pm 0.0507 N=19	3.7590 \pm 0.0592 N=14
Female	18 months	20.122 \pm 0.800 N=16	21.75 \pm 1.19 N=13	3.7547 \pm 0.0613 N=16	3.7539 \pm 0.0733 N=13
Male		20.716 \pm 0.978 N=12	19.145 \pm 0.919 N=12	3.6609 \pm 0.0784 N=12	3.5930 \pm 0.0594 N=12
Genotype		F _(1,103) =0.03, p=0.860		F _(1,103) =0.48, p=0.489	
Sex		F _(1,103) =0.09, p=0.767		F _(1,103) =0.00, p=0.991	

Genotype*Sex	$F_{(1,103)}=2.04, p=0.156$	$F_{(1,103)}=2.28, p=0.134$
Cohort	$F_{(1,103)}=0.50, p=0.479$	$F_{(1,103)}=0.87, p=0.352$
Weight	$F_{(1,103)}=2.55, p=0.113$	$F_{(1,103)}=2.08, p=0.152$
Weight*Sex	$F_{(1,103)}=0.18, p=0.673$	$F_{(1,103)}=0.01, p=0.914$
Weight*Cohort	$F_{(1,103)}=0.26, p=0.613$	$F_{(1,103)}=0.32, p=0.573$
Weight*Genotype	$F_{(1,103)}=0.06, p=0.807$	$F_{(1,103)}=0.57, p=0.450$
Sex*Cohort	$F_{(1,103)}=0.49, p=0.483$	$F_{(1,103)}=0.30, p=0.583$
Genotype*Cohort	$F_{(1,103)}=0.49, p=0.486$	$F_{(1,103)}=0.03, p=0.859$

Table S11: Descriptive statistics of forefoot swing speed and forefoot stride length for *MacroD1* from the catwalk gait analysis. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. Statistics was performed on all factors combined using a factorial-ANOVA.

<i>MacroD1</i> Catwalk	<i>Forefoot Swing Speed (cm/s)</i>			<i>Forefoot Stride Length (cm)</i>	
	AGE	WT	<i>MacroD1</i> KO	WT	<i>MacroD1</i> KO
Female	12 months	54.34 \pm 1.81 N=13	56.94 \pm 3.08 N=15	5.995 \pm 0.188 N=13	6.065 \pm 0.191 N=15
Male		51.96 \pm 1.03 N=19	52.26 \pm 1.96 N=14	5.856 \pm 0.126 N=19	5.813 \pm 0.175 N=14
Female	18 months	50.92 \pm 1.66 N=16	53.16 \pm 2.26 N=13	6.134 \pm 0.128 N=16	6.058 \pm 0.138 N=13
Male		54.89 \pm 1.87 N=12	49.08 \pm 1.91 N=12	6.081 \pm 0.170 N=12	5.736 \pm 0.181 N=12
Genotype	$F_{(1,103)}=0.35, p=0.558$			$F_{(1,103)}=0.01, p=0.939$	
Sex	$F_{(1,103)}=0.01, p=0.905$			$F_{(1,103)}=1.50, p=0.223$	
Genotype*Sex	$F_{(1,103)}=2.82, p=0.096$			$F_{(1,103)}=0.44, p=0.508$	
Cohort	$F_{(1,103)}=0.50, p=0.479$			$F_{(1,103)}=0.05, p=0.827$	
Weight	$F_{(1,103)}=0.00, p=0.970$			$F_{(1,103)}=0.52, p=0.473$	
Weight*Sex	$F_{(1,103)}=0.08, p=0.780$			$F_{(1,103)}=1.85, p=0.177$	
Weight*Cohort	$F_{(1,103)}=0.28, p=0.597$			$F_{(1,103)}=0.00, p=0.949$	
Weight*Genotype	$F_{(1,103)}=0.34, p=0.561$			$F_{(1,103)}=0.05, p=0.817$	
Sex*Cohort	$F_{(1,103)}=0.37, p=0.547$			$F_{(1,103)}=0.44, p=0.510$	
Genotype*Cohort	$F_{(1,103)}=1.40, p=0.240$			$F_{(1,103)}=0.51, p=0.476$	

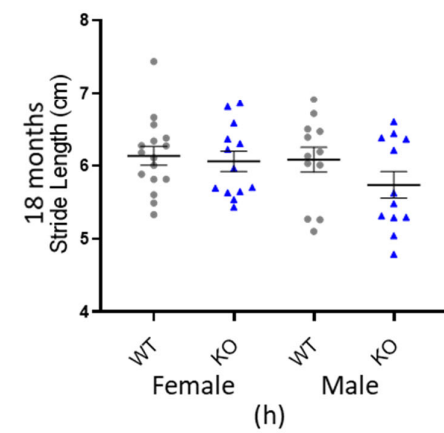
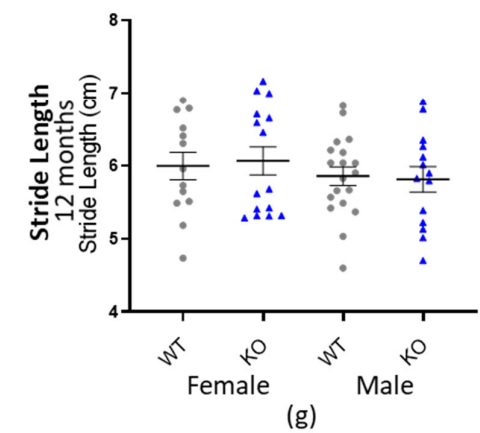
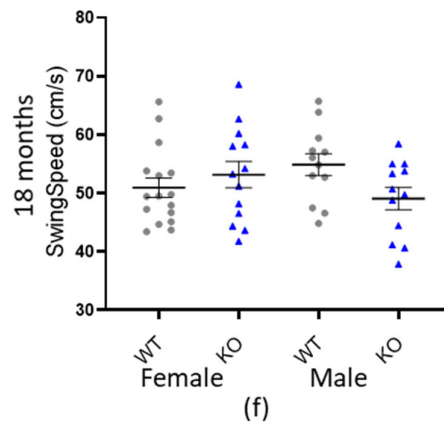
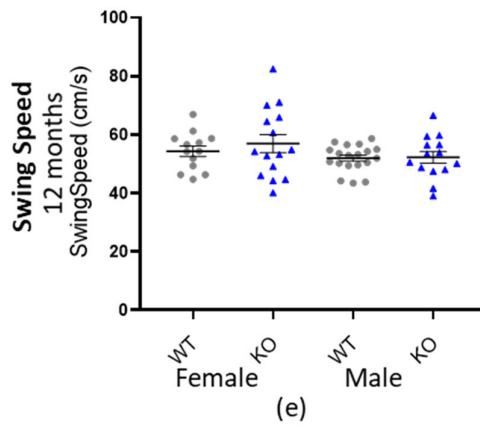
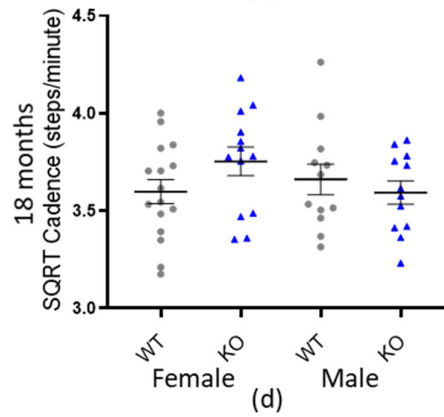
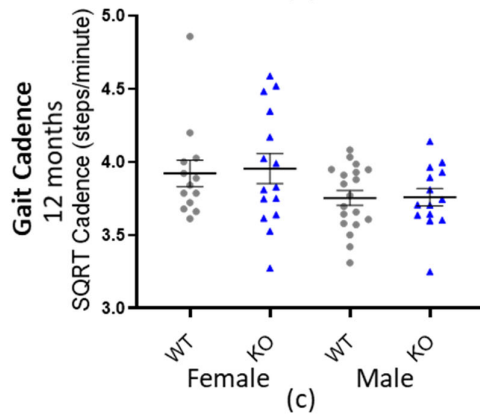
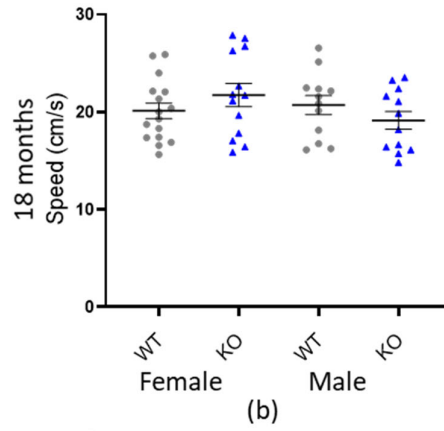
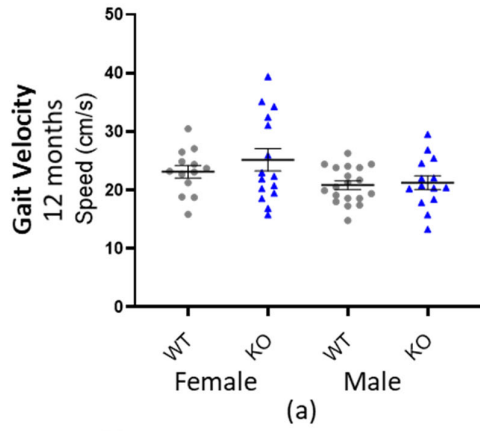


Figure S9: *Macro1* KO is not associated an altered gait. Results from catwalk gait analysis. Graphs show individual values dot plot, WT shown in grey circles and *Macro1* KO in blue triangles. SQRT = Square-root transformed. Error bars are the SEM. Graphs are as follows, **a-b**) gait velocity (average speed cm/s) at 12 and 18 months, **c-d**) SQRT gait cadence (steps/minute) at 12 and 18 months, **e-f**) Forefoot swing speed (cm/s) at 12 and 18 months, and **g-h**) forefoot stride length (cm) at 12 and 18 months.

Table S12: Descriptive statistics of SQRT-fore and hind paw intensity for *Macro2* from the catwalk gait analysis. SQRT = square root transformed. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. *Macro2* used a factorial-ANOVA with repeated measures, hence the term Mouse name. x = not an exact F-test.

<i>Macro2</i> Catwalk	SQRT-Forepaw Intensity (arbitrary)			SQRT-Hind Paw Intensity (arbitrary)	
	AGE	WT	<i>Macro1</i> KO	WT	<i>Macro1</i> KO
Female	3 months	8.6722 \pm 0.0346 N=20	8.6733 \pm 0.0522 N=17	8.9759 \pm 0.0616 N=20	9.0381 \pm 0.0578 N=17
Male		8.9180 \pm 0.0705 N=13	8.8875 \pm 0.0400 N=17	9.0652 \pm 0.0811 N=13	9.1627 \pm 0.0794 N=17
Female	13 months	8.1452 \pm 0.0979 N=16	8.4966 \pm 0.0942 N=16	7.959 \pm 0.140 N=16	8.657 \pm 0.116 N=16
Male		8.716 \pm 0.104 N=13	8.302 \pm 0.100 N=17	8.557 \pm 0.137 N=13	8.230 \pm 0.147 N=17
Genotype	F _(1,54) =0.46, p=0.501 x			F _(1,54) =1.54, p=0.219 x	
Sex	F _(1,54) =0.56, p=0.456 x			F _(1,54) =0.56, p=0.456 x	
Genotype*Sex	F _(1,54) =8.31, *p=0.005 x			F _(1,54) =7.47, p=0.008 x	
Cohort	F _(1,54) =1.99, p=0.164			F _(1,54) =3.79, p=0.057	
Weight	F _(1,54) =1.19, p=0.280			F _(1,54) =0.01, p=0.935	
Weight*Sex	F _(1,54) =0.51, p=0.479			F _(1,54) =0.04, p=0.835	
Weight*Cohort	F _(1,54) =0.20, p=0.657			F _(1,54) =1.06, p=0.309	
Sex*Cohort	F _(1,54) =1.21, p=0.276			F _(1,54) =0.81, p=0.373	
Genotype*Cohort	F _(1,54) =0.01, p=0.936			F _(1,54) =1.80, p=0.186	
Mouse Name	F _(1,54) =0.96, p=0.558			F _(1,54) =1.30, p=0.158	

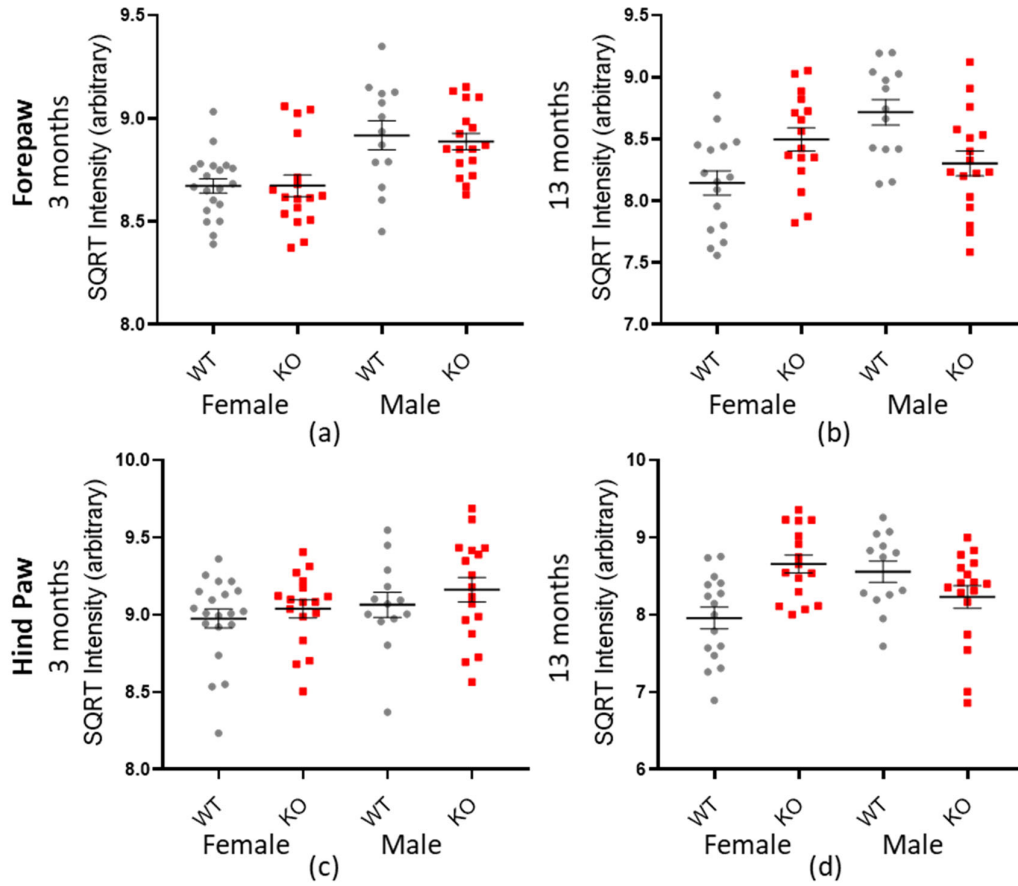


Figure S10: *MacroD2* KO is not associated with changes in fore or hind paw foot pressure. Results from catwalk gait analysis. Graphs show individual values dot plot, WT shown in grey circles and *MacroD2* KO in red squares. SQRT = Square root transformed. Error bars are the SEM. Graphs are as follows, **a-b**) forepaw intensity at 3 and 13 months, **c-d**) hind paw intensity at 3 and 13 months.

Table S13: Descriptive statistics of *MacroD1* grip strength. Results from 4 limb hang test. SQRT = square root transformed. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. Statistics was performed on all factors combined using a factorial-ANOVA.

<i>MacroD1</i> Grip Strength	SQRT Hanging Impulse (gs)		
	AGE	WT	<i>MacroD1</i> KO
Female	12 months	76.94 \pm 6.68 N=13	79.72 \pm 4.54 N=17
Male		60.14 \pm 3.80 N=19	63.85 \pm 5.03 N=15
Female	18 months	40.27 \pm 1.75 N=17	45.98 \pm 4.25 N=15
Male		35.13 \pm 3.21 N=12	43.06 \pm 3.27 N=12
Genotype		F _(1,109) =0.51, p=0.477	
Sex		F _(1,109) =1.05, p=0.307	
Genotype*Sex		F _(1,109) =0.40, p=0.529	
Cohort		F _(1,109) =19.89, *p > 0.001	
Weight		F _(1,109) =25.43, *p > 0.001	
Weight*Sex		F _(1,109) =1.44, p=0.234	
Weight*Cohort		F _(1,109) =11.92, *p=0.001	
Weight*Genotype		F _(1,109) =0.76, p=0.384	
Sex*Cohort		F _(1,109) =1.28, p=0.261	
Genotype*Cohort		F _(1,109) =0.19, p=0.662	

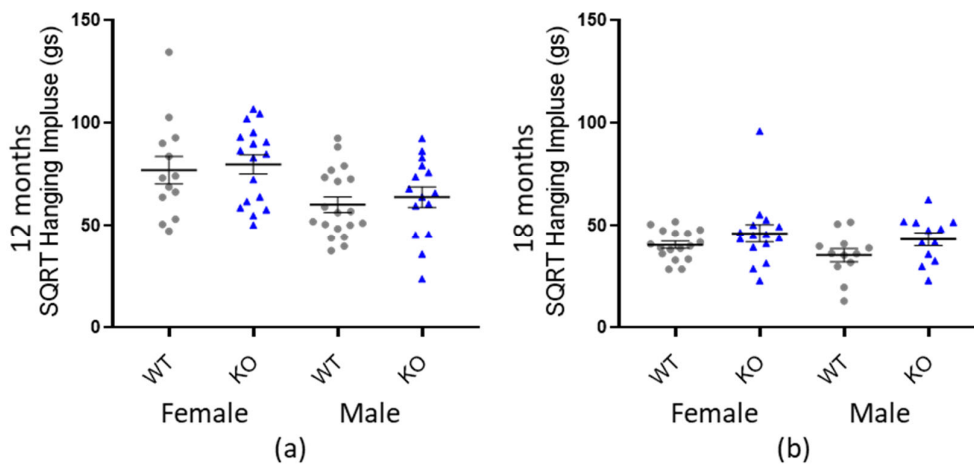


Figure S11: *MacroD1* KO is not associated altered grip strength. Results from 4 limb hang test. Graphs show individual values dot plot, WT shown in grey circles and *MacroD1* KO in blue triangles. SQRT = Square root transformed. Error bars are the SEM. Graphs are as follows, **a-b** SQRT hanging impulse (gs) at 12 and 18 months.

Table 14: Descriptive statistics of *Macro2* grip strength. Results from link lifting test. Mean \pm SEM is presented. Individual N number is included as well as p-values for all terms and interactions. *Macro2* used a factorial-ANOVA with repeated measures, hence the term Mouse name. x = not an exact F-test.

<i>Macro2</i> Grip Strength	<i>Lift Score (out of 20)</i>		
	AGE	WT	<i>Macro2</i> KO
Female	3 months	9.606 \pm 0.963 N=20	11.149 \pm 0.927 N=17
Male		7.995 \pm 0.818 N=13	8.082 \pm 0.578 N=16
Female	13 months	5.407 \pm 0.820 N=16	6.45 \pm 1.01 N=16
Male		5.464 \pm 0.404 N=13	4.900 \pm 0.289 N=17
Genotype		F _(1,53) =0.03, p=0.866 x	
Sex		F _(1,53) =0.13, p=0.721 x	
Genotype*Sex		F _(1,53) =1.69, p=0.198 x	
Cohort		F _(1,53) =3.26, p=0.077	
Weight		F _(1,53) =1.83, p=0.182	
Weight*Sex		F _(1,53) =0.04, p=0.846	
Weight*Cohort		F _(1,53) =1.94, p=0.170	
Sex*Cohort		F _(1,53) =0.19, p=0.667	
Genotype*Cohort		F _(1,53) =0.50, p=0.483	
Mouse name		F _(1,53) =1.55, p=0.052	

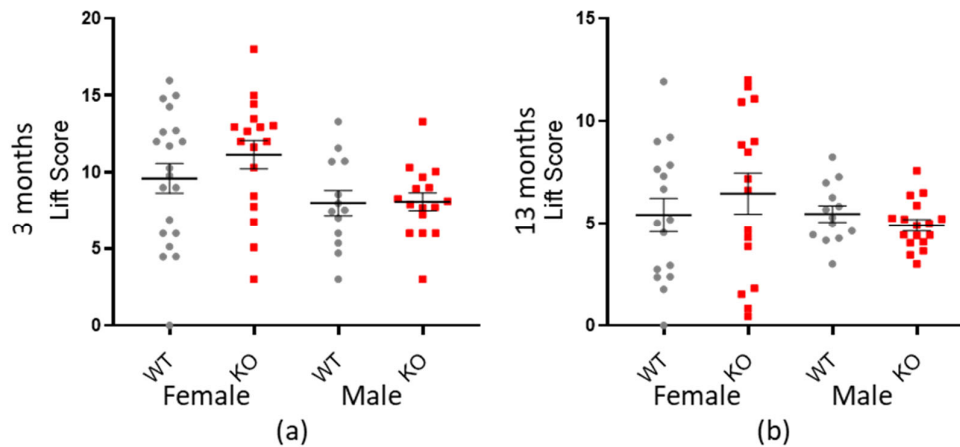


Figure S12: *Macro2* KO is not associated altered grip strength. Results from link lifting test. Graphs show individual values dot plot, WT shown in grey circles and *Macro2* KO in red squares. Error bars are the SEM. Graphs are as follows, **a-b)** Lift score at 3 and 13 months.