

## Supplementary data

Table S1. Physical performance in males and females Naïve 12-month-old 3xTg-AD and NTg mice.

Functional Profile	Males		Females		Statistics
	NTg mice <i>n</i> =13 (Mean ± SEM)	3xTg-AD mice <i>n</i> =19 (Mean ± SEM)	NTg mice <i>n</i> =17 (Mean ± SEM)	3xTg-AD mice <i>n</i> =14 (Mean ± SEM)	
Bodyweight	29.31 ± 0.56	35.67 ± 1.79 <i>p</i> = 0.039 <sup>s</sup>	27.15 ± 1.12	33.93 ± 2.14 <i>p</i> = 0.024 <sup>s</sup>	<i>G</i> , <i>p</i> < 0.001***
<b>Quantitative parameters of gait - Gait</b>					
Stride length (cm)	5.00 ± 0.36	4.25 ± 0.46	4.28 ± 0.35	5.19 ± 0.26	<i>GxS</i> , <i>p</i> = 0.037*
Variability of stride length (%)	33.60 ± 3.00	30.47 ± 3.59	30.28 ± 3.00	19.53 ± 2.98	<i>S</i> , <i>p</i> = 0.015*
Speed (cm/s)	10.78 ± 2.10	5.34 ± 1.01 <i>p</i> = 0.018 <sup>s</sup>	8.10 ± 1.87	6.71 ± 1.10	<i>GxS</i> , <i>p</i> = 0.033* <i>S</i> , <i>p</i> = 0.015*
Cadence (steps/s)	3.76 ± 0.62	1.86 ± 0.35 <i>p</i> = 0.007 <sup>ss</sup>	3.28 ± 0.72	1.52 ± 0.26	<i>G</i> , <i>p</i> = 0.002**
<b>Exploration and Neophobia – Corner test</b>					
Horizontal activity ( <i>n</i> corners)	9.15 ± 0.85	8.74 ± 1.32	9.13 ± 0.98	9.58 ± 1.43	<i>n.s.</i>
Vertical activity ( <i>n</i> rearings)	2.85 ± 0.89	2.16 ± 0.59	2.13 ± 0.53	2.36 ± 0.54	<i>n.s.</i>
Rearing latency (s)	39.46 ± 6.15	32.31 ± 5.30	31.54 ± 4.74	29.37 ± 5.26	<i>n.s.</i>
Ratio (corners/rearings)	2.02 ± 0.73	2.53 ± 0.69	3.95 ± 0.93	5.38 ± 1.26	<i>S</i> , <i>p</i> = 0.015*
Freezing (movement latency, s)	0.94 ± 0.49	5.69 ± 3.21	4.64 ± 3.73	1.34 ± 0.65	<i>n.s.</i>
<b>Response to gravity- Geotaxis</b>					
Geotaxis (latency, s)	5.77 ± 0.65	4.61 ± 0.64	4.61 ± 0.39	6.21 ± 0.60	<i>GxS</i> *
<b>Motor performance - Rotarod</b>					
Motor learning (latency, s)	29.23 ± 6.58	18.79 ± 4.55	45.53 ± 5.73	32.00 ± 6.79	<i>S</i> *
Motor learning - (trials learning)	2.54 ± 0.42	3.37 ± 0.44	1.82 ± 0.35	1.86 ± 0.27 <i>p</i> = 0.010 <sup>z</sup>	<i>S</i> , <i>p</i> = 0.004**
Physical endurance (total latency, s)	216.35 ± 15.28	144.03 ± 13.83 <i>p</i> = 0.001 <sup>ss</sup>	182.30 ± 9.99	200.76 ± 13.50 <i>p</i> = 0.014 <sup>z</sup>	<i>GxS</i> , <i>p</i> = 0.001** <sup>z</sup>
Day 1 (total latency, s)	141.68 ± 15.25	91.46 ± 9.05 <i>p</i> = 0.020 <sup>s</sup>	116.49 ± 10.19	122.40 ± 12.19	<i>GxS</i> , <i>p</i> = 0.019*
Day 2 (total latency, s)	245.85 ± 18.40	151.75 ± 18.47 <i>p</i> = 0.001 <sup>ss</sup>	206.91 ± 13.31	213.79 ± 17.78	<i>G</i> , <i>p</i> = 0.012*, <i>GxS</i> , <i>p</i> = 0.004**
Day 3 (total latency, s)	261.53 ± 17.45	188.89 ± 17.26 <i>p</i> = 0.014 <sup>s</sup>	223.50 ± 12.91	266.10 ± 17.71 <i>p</i> = 0.006 <sup>z</sup>	<i>GxS</i> , <i>p</i> = 0.001**

*G*, Genotype effect, *G*\*\*\* *p* < 0.001, *G*\*\* *p* < 0.01, *G*\* *p* < 0.05, *n.s.* *p* > 0.05. *S*, Sex effect, *S*\*\*\* *p* < 0.001, *S*\*\* *p* < 0.01, *S*\* *p* < 0.05, *n.s.* *p* > 0.05. *GxS*, genotype and sex interaction effects, *GxS*\*\*\* *p* < 0.01, *GxS*\*\* *p* < 0.05, *GxS*\* *p* < 0.05, *n.s.* *p* > 0.05. Bonferroni *post hoc* test: *g*, genotype; *s*, sex; and *z* expressed genotype differences between sex, and *#* expressed sex differences between genotypes.

Table S2. Physical performance in males and female 3xTg-AD and NTg after Re-test to 16m.

Functional Profile	Males		Females		Statistics	
	NTg mice <i>n</i> =10 (Mean ± SEM)	3xTg-AD mice <i>n</i> =14 (Mean ± SEM)	NTg mice <i>n</i> =12 (Mean ± SEM)	3xTg-AD mice <i>n</i> =9 (Mean ± SEM)	ANOVA (Retest)	MRA (12m vs. 16m)
Bodyweight	29.09 ± 0.40	33.63 ± 1.55 <i>p</i> = 0.035 <sup>s</sup>	25.65 ± 0.78	26.37 ± 0.80 <i>p</i> < 0.001 <sup>‡</sup>	<i>G</i> , <i>p</i> = 0.026*	<i>G</i> , <i>p</i> = 0.041* <i>S</i> , <i>p</i> = 0.003**
<i>S</i> , <i>p</i> < 0.001**						
Quantitative parameters of gait - Gait						
Stride length (cm)	3.61 ± 0.41	2.96 ± 0.49 <i>p</i> = 0.023 <sup>s</sup>	3.03 ± 0.49	4.63 ± 0.49	<i>GxS</i> , <i>p</i> = 0.017*	<i>n.s.</i>
Variability of stride length (%)	22.18 ± 4.23	30.50 ± 5.53	27.61 ± 6.09	18.53 ± 2.15	<i>n.s.</i>	<i>S</i> , <i>p</i> = 0.026*
Speed (cm/s)	6.85 ± 1.33	2.69 ± 0.79 <i>p</i> = 0.026 <sup>s</sup>	5.48 ± 1.31	7.36 ± 1.35	<i>GxS</i> , <i>p</i> = 0.042*	<i>n.s.</i>
Cadence (steps/s)	3.04 ± 0.53	2.24 ± 0.36 <i>p</i> = 0.004 <sup>s</sup>	2.83 ± 0.67	2.39 ± 0.51	<i>n.s.</i>	<i>G</i> , <i>p</i> = 0.011*
Exploration and Neophobia – Corner test						
Horizontal activity ( <i>n</i> corners)	8.70 ± 1.88	6.92 ± 1.48	6.82 ± 1.88	11.56 ± 2.70	<i>n.s.</i>	<i>n.s.</i>
Vertical activity ( <i>n</i> corners)	1.50 ± 0.87	0.38 ± 0.30	0.82 ± 0.64	1.44 ± 0.56	<i>n.s.</i>	<i>n.s.</i>
Rearing latency (s)	38.11 ± 7.77	53.38 ± 2.83	51.48 ± 5.78	36.70 ± 7.82	<i>n.s.</i>	<i>n.s.</i>
Ratio (corners/rearings)	2.95 ± 1.82	1.19 ± 0.68	0.54 ± 0.42	5.02 ± 2.02	<i>GxS</i> , <i>p</i> = 0.037* <i>GxS</i> , <i>p</i> = 0.008 <sup>‡‡</sup>	<i>GxS</i> , <i>p</i> = 0.007**
Freezing (movement latency, s)	7.67 ± 5.87	10.60 ± 6.88	11.19 ± 7.28	0.88 ± 0.58	<i>n.s.</i>	<i>n.s.</i>
Response to gravity- Geotaxis						
Geotaxis (latency, s)	4.95 ± 0.83	7.75 ± 1.03 <i>p</i> = 0.042 <sup>r</sup>	6.61 ± 1.02	5.87 ± 1.01	<i>GxS</i> , <i>p</i> = 0.012*	<i>n.s.</i>
Motor performance - Rotarod						
Motor learning (latency, s)	39.00 ± 8.65	56.64 ± 3.13 <i>p</i> < 0.001 <sup>rrr</sup> <i>p</i> = 0.025 <sup>s</sup>	60.00 ± 0.00	60.00 ± 0.00	<i>G</i> , <i>p</i> = 0.042*, <i>GxS</i> , <i>p</i> = 0.042*	<i>S</i> , <i>p</i> = 0.021*
Motor learning (trials learning)	1.60 ± 0.26	1.15 ± 0.10	1.00 ± 0.00	1.00 ± 0.00 <i>p</i> = 0.019 <sup>‡</sup>	<i>S</i> , <i>p</i> = 0.07**	<i>S</i> , <i>p</i> = 0.024*
Physical endurance (latency, s)	228.43 ± 10.27	184.04 ± 15.60	209.64 ± 18.58	257.94 ± 20.07 <i>p</i> = 0.010 <sup>‡</sup>	<i>GxS</i> , <i>p</i> = 0.005**	<i>GxS</i> , <i>p</i> = 0.005**
Day 1 (total latency, s)	179.48 ± 14.89	141.9 ± 11.29	176.63 ± 18.66	188.15 ± 23.17	<i>n.s.</i>	<i>n.s.</i>
Day 2 (total latency, s)	250.09 ± 14.13	189.44 ± 17.42	222.13 ± 21.83	282.93 ± 27.78 <i>p</i> = 0.008 <sup>‡‡</sup>	<i>GxS</i> , <i>p</i> = 0.003**	<i>GxS</i> , <i>p</i> = 0.004**
Day 3 (total latency, s)	255.72 ± 11.86	220.9 ± 20.71	229.87 ± 20.49	302.76 ± 20.27 <i>p</i> = 0.017 <sup>‡</sup>	<i>GxS</i> , <i>p</i> = 0.006**	<i>GxS</i> , <i>p</i> = 0.003**

MRA, naïve 12m - retest 16m, ANOVA. *G*, Genotype effect, *G*\*\*\* *p* < 0.01, *G*\*\* *p* < 0.05, *G*\* *p* < 0.05, *n.s.* *p* > 0.05. *S*, Sex effect, *S*\*\*\* *p* < 0.01, *S*\*\* *p* < 0.05, *S*\* *p* < 0.05, *n.s.* *p* > 0.05. *GxS*, genotype and sex interaction effects, *GxS*\*\*\* *p* < 0.01, *GxS*\*\* *p* < 0.05, *GxS*\* *p* < 0.05, *n.s.* *p* > 0.05. Bonferroni *post hoc* test: *g*, genotype; *s*, sex; and \$ expressed genotype differences between sex, and # expressed sex differences between genotypes, and r expressed re-test differences between 12m and 16m in the same group.

Table S3. Physical performance in males and females Naïve 16-month-old 3xTg-AD and NTg mice.

Functional Profile	Males		Females		Statistics	
	NTg mice <i>n</i> =12 (Mean ± SEM)	3xTg-AD mice <i>n</i> =12 (Mean ± SEM)	NTg mice - (Mean ± SEM)	3xTg-AD mice <i>n</i> =9 (Mean ± SEM)	ANOVA Naïve 16m	ANOVA Naïve vs. Retest
<b>Bodyweight</b> <i>s, p &lt; 0.001***</i>	31.53 ± 0.90	36.44 ± 1.81 <i>p = 0.023<sup>s</sup></i>	-	26.90 ± 0.40 <i>p &lt; 0.001<sup>z</sup></i>	<b>G, <i>p</i> = 0.001**</b>	<b>R, <i>p</i> = 0.006**</b> <b>g, <i>p</i> = 0.005<sup>ss</sup></b> <b>s, <i>p</i> &lt; 0.001<sup>***</sup></b>
<b>Quantitative parameters of gait - Gait</b>						
Stride length (cm)	4.59 ± 0.42	4.80 ± 0.50	-	4.51 ± 0.58	<i>n.s.</i>	<i>N, p = 0.023<sup>r</sup></i> <i>NxS, p = 0.047<sup>z</sup></i>
Variability of stride length (%)	25.53 ± 2.71	25.79 ± 3.92	-	20.25 ± 4.46 <i>p = 0.026<sup>z</sup></i>	<i>n.s.</i>	<i>S, p = 0.026<sup>z</sup></i>
Speed (cm/s)	3.54 ± 0.91	2.93 ± 0.47	-	5.72 ± 1.83	<i>n.s.</i>	<i>G, p = 0.022<sup>s</sup></i> <i>S, p = 0.014<sup>z</sup></i>
Cadence (steps/s)	1.24 ± 0.16 <i>p = 0.037<sup>r</sup></i>	0.80 ± 0.09	-	1.72 ± 0.67	<i>n.s.</i>	<i>G, p = 0.001<sup>ss</sup></i> <i>R, p = 0.016<sup>r</sup></i>
<b>Exploration and Neophobia – Corner test</b>						
Horizontal activity ( <i>n</i> corners)	8.33 ± 0.80	10.25 ± 1.95	-	10.11 ± 2.62	<i>n.s.</i>	<i>n.s.</i>
Vertical activity ( <i>n</i> rearings)	2.58 ± 0.86	3.75 ± 1.11	-	1.33 ± 0.50	<i>n.s.</i>	<i>N, p = 0.005<sup>ss</sup></i> <i>N, p = 0.044<sup>z</sup></i> <i>NxS, p = 0.023<sup>z</sup></i>
Rearing latency (s)	27.44 ± 7.23	32.69 ± 7.15	-	36.30 ± 7.90	<i>n.s.</i>	<i>N, p = 0.022<sup>s</sup></i>
Ratio (corners/rearings)	1.85 ± 0.51	1.44 ± 0.41	-	4.35 ± 2.22	<i>n.s.</i>	<i>N, p = 0.039<sup>s</sup></i>
Freezing (movement latency, s)	0.09 ± 0.09	1.04 ± 0.64	-	14.05 ± 8.70	<i>n.s.</i>	<i>N, p = 0.013<sup>s</sup></i>
<b>Response to gravity- Geotaxis</b>						
Geotaxis (latency, s)	5.47 ± 0.99	4.24 ± 0.49 <i>p = 0.041<sup>r</sup></i>	-	8.21 ± 1.14	<i>n.s.</i>	<i>GxR, p = 0.009**</i> <i>GxS, p = 0.002**</i>
<b>Motor performance – Rotarod</b>						
Motor learning (latency, s)	44.08 ± 6.55	29.08 ± 6.99 <i>p = 0.007<sup>mn</sup></i>	-	30.33 ± 8.34 <i>p = 0.026<sup>n</sup></i> <i>p &lt; 0.001<sup>***</sup></i>	<i>n.s.</i>	<i>GxR, p = 0.014<sup>s</sup></i>
Motor learning (trials learning)	1.58 ± 0.22	2.08 ± 0.28 <i>p = 0.012<sup>n</sup></i>	-	3.00 ± 0.85 <i>p = 0.022<sup>n</sup></i> <i>p &lt; 0.001<sup>***</sup></i>	<i>n.s.</i>	<i>R, p = 0.042<sup>s</sup></i> <i>GxR, p = 0.042*</i>
Physical endurance (total latency, s)	177.62 ± 12.01 <i>p &lt; 0.001<sup>aaa</sup></i> <i>p &lt; 0.001<sup>mm</sup></i>	189.27 ± 11.56 <i>p = 0.001<sup>mn</sup></i>	-	206.58 ± 21.47 <i>p = 0.001<sup>nn</sup></i> <i>p = 0.001<sup>aa</sup></i>	<i>n.s.</i>	<i>R, p &lt; 0.001<sup>sss</sup></i> <i>R, p &lt; 0.001<sup>***</sup></i> <i>S, p = 0.004<sup>zz</sup></i>
Day 1 (total latency, s)	110.09 ± 9.66	118.65 ± 9.31 <i>p &lt; 0.001<sup>aaa</sup></i> <i>p = 0.025<sup>n</sup></i>	-	147.44 ± 24.10	<i>n.s.</i>	<i>R, p = 0.006<sup>ss</sup></i> <i>S, p = 0.022<sup>z</sup></i>
Day 2 (total latency, s)	199.23 ± 16.02	208.43 ± 14.56 <i>p &lt; 0.004<sup>aa</sup></i>	-	217.17 ± 23.20	<i>n.s.</i>	<i>S, p = 0.017<sup>z</sup></i>
Day 3 (total latency, s)	223.54 ± 17.86 <i>p = 0.009<sup>aa</sup></i>	240.73 ± 15.31	-	255.13 ± 30.47 <i>p = 0.013<sup>n</sup></i>	<i>n.s.</i>	<i>R, p = 0.001<sup>ss</sup></i> <i>R, p = 0.001<sup>zz</sup></i>

$$p = 0.008^{***}$$

$$S, p = 0.011^{\#}$$

G, Genotype effect,  $G^* p < 0.05$ , *n.s.*  $p > 0.05$ . S, Sex effect,  $S^{***} p < 0.01$ ,  $S^{**} p < 0.05$ , *n.s.*  $p > 0.05$ . Bonferroni *post hoc* test: s, sex; and # expressed sex differences between genotypes; \$ expressed genotype differences between sex, and # expressed sex differences between genotypes; a expressed age differences in each group; r expressed re-test differences between 12m and 16m in the same group, and n expressed naïve differences between re-test 16m and naïve16m in the same group.

**Table S4: Statistics Figure 5C**

Figure 5C.1 Males: MRA -ANOVA, Day-by-day1, $F(5,74) = 6.779$ , $p < 0.001$ , <i>post hoc</i> NTg naïve 12m vs. 3xTg-AD naïve 12m $p = 0.023$ , NTg naïve 16m vs. NTg re-test 16m $p = 0.012$ , 3xTg-AD naïve 12m vs. 3xTg-AD re-test 16m $p = 0.002$ . Genotype differences, MRA-ANOVA, $F(1,76) = 4.638$ , $p = 0.034$ . Re-test differences, MRA-ANOVA, $F(1,76) = 20.040$ , $p < 0.001$ .
Figure 5C.2 Males: MRA -ANOVA, Day-by-day 2, $F(5,73) = 5.078$ , $p < 0.001$ , <i>post hoc</i> naïve 12-month-old NTg vs. naïve 3xTg-AD 12m $p = 0.001$ . Genotype differences, MRA-ANOVA, $F(1,75) = 11.412$ , $p = 0.01$ .
Figure 5C.3 Males: MRA -ANOVA, Day-by-day 3, $F(5,73) = 2.733$ , $p = 0.026$ , <i>post hoc</i> naïve NTg 12m vs. naïve 3xTg-AD 12m $p = 0.028$ . Genotype differences, MRA-ANOVA, $F(1,75) = 4.480$ , $p = 0.038$ .
Figure 5C.4 Males: MRA -ANOVA, Trial-by-trial, $F(5,73) = 5.211$ , $p < 0.001$ . Genotype differences, MRA-ANOVA, $F(1,75) = 8.815$ , $p = 0.004$ . Re-test differences, MRA-ANOVA, $F(1,75) = 4.692$ , $p = 0.033$ .
Figure 5C.5 Females: MRA -ANOVA, Trial-by-trial, $F(4,65) = 3.137$ , $p = 0.021$ , <i>post hoc</i> NTg naïve 12m vs. 3xTg-AD re-test 16m $p = 0.009$ .
Figure 5C.6 Females: MRA -ANOVA, Day-by-day 1, $F(4,56) = 4.438$ , $p = 0.03$ , <i>post hoc</i> NTg naïve 12m vs. NTg re-test 16m $p = 0.028$ , NTg naïve 12m vs. re-test 3xTg-AD 16m $p = 0.025$ .
Figure 5C.7 Females: MRA -ANOVA, Day-by-day 3, $F(4,56) = 2.701$ , $p = 0.040$ .
Figure 6C.8 3xRg-AD: MRA -ANOVA, Trial-by-trial, Trial by trial: MRA-ANOVA, $F(5,71) = 5.586$ , $p < 0.001$ . Sex differences, MRA-ANOVA, $F(1,73) = 15.213$ , $p < 0.001$ . Re-test differences, MRA-ANOVA, $F(1,73) = 7.873$ , $p = 0.006$ .
Figure 5C.9 3xTg-AD: MRA -ANOVA, Day-by-day 1, $F(5,71) = 5.424$ , $p < 0.001$ , <i>post hoc</i> females re-test 16m vs. naïve males 12m $p < 0.001$ , re-test females 16m vs. 16m naïve males $p = 0.042$ . Sex differences: MRA-ANOVA, $F(1,73) = 6.537$ , $p = 0.013$ . Re-test differences: MRA-ANOVA, $F(1,73) = 16.327$ , $p < 0.001$ .
Figure 5C.10 3xTg-AD: MRA -ANOVA, Day-by-day 2, $F(5,71) = 4.694$ , $p = 0.001$ , <i>post hoc</i> females re-test 16m vs. naïve males 12m $p < 0.001$ , re-test females 16m vs. 16m naïve males $p = 0.036$ . Sex differences: MRA-ANOVA, $F(1,73) = 14.001$ , $p < 0.001$ . Re-test differences: MRA-ANOVA, $F(1,73) = 5.371$ , $p = 0.023$ .
Figure 5C.11 3xTg-AD: MRA -ANOVA, Day-by-day 3, $F(5,71) = 4.077$ , $p = 0.003$ , <i>post hoc</i> females re-test 16m vs. naïve males 12m $p = 0.002$ . Sex differences: MRA-ANOVA, $F(1,73) = 13.723$ , $p < 0.001$ .
Figure 5C.12 Males - Day 1: T1, ANOVA, $F(5,74) = 4.931$ , $p = 0.001$ , <i>post hoc</i> naïve 3xTg-AD 12m vs. 3xTg-AD re-test 16m $p = 0.004$ ; Re-test differences, ANOVA, $F(1,78) = 18.084$ , $p < 0.001$ . T2, ANOVA, $F(5,74) = 4.260$ , $p = 0.002$ , <i>post hoc</i> naïve 3xTg-AD 12m vs. 3xTg-AD re-test 16m $p = 0.007$ ; Re-test differences, ANOVA, $F(1,78) = 18.307$ , $p < 0.001$ . T3, ANOVA, $F(5,74) = 3.981$ , $p = 0.003$ , <i>post hoc</i> naïve 3xTg-AD 12m vs. 3xTg-AD re-test 16m $p = 0.011$ ; Re-test differences, ANOVA, $F(1,78) = 12.376$ , $p = 0.001$ . T4, ANOVA, $F(5,74) = 5.452$ , $p < 0.001$ , <i>post hoc</i> NTg re-test 16m vs. naïve NTg 16m $p = 0.003$ , 3xTg-AD naïve 16m vs. NTg naïve 16m $p = 0.005$ ; Genotype differences, ANOVA, $F(1,78) = 11.578$ , $p = 0.001$ ; Re-test differences, ANOVA, $F(1,78) = 12.228$ , $p = 0.001$ . T5, ANOVA, $F(5,74) = 4.868$ , $p = 0.001$ , <i>post hoc</i> NTg re-test 16m vs. naïve NTg 16m $p = 0.016$ , 3xTg-AD naïve 12m vs. 3xTg-AD re-test 16m $p = 0.025$ ; Re-test differences, ANOVA, $F(1,78) = 16.546$ , $p < 0.001$ . T6, ANOVA, $F(5,74) = 5.916$ , $p < 0.001$ , <i>post hoc</i> 3xTg-AD naïve 12m vs. NTg

naïve 12m  $p = 0.002$ , 3xTg-AD naïve 12m vs. 3xTg-AD re-test 16m  $p = 0.006$ ; Genotype differences, ANOVA  $F(1,78) = 8.355$ ,  $p = 0.005$ ; Re-test differences, ANOVA,  $F(1,78) = 11.347$ ,  $p = 0.001$ .

#### Figure 5C.13

Males - Day 2: T1, ANOVA,  $F(5,74) = 2.963$ ,  $p = 0.027$ , *post hoc* 3xTg-AD naïve 12m vs. NTg naïve 12m  $p = 0.017$ ; Genotype differences, ANOVA,  $F(1,78) = 4.168$ ,  $p = 0.045$ . T3, ANOVA,  $F(5,74) = 5.098$ , *post hoc* 3xTg-AD naïve 12m vs. NTg naïve 12m  $p = 0.002$ ; Genotype differences, ANOVA,  $F(1,78) = 8.601$ ,  $p = 0.004$ . T4, ANOVA,  $F(5,74) = 5.807$ ,  $p < 0.001$ , *post hoc* 3xTg-AD naïve 12m vs. NTg naïve 12m  $p = 0.001$ ; Genotype differences, ANOVA,  $F(1,78) = 12.959$ ,  $p = 0.001$ . T5, ANOVA,  $F(5,74) = 8.099$ ,  $p < 0.001$ , *post hoc* 3xTg-AD naïve 12m vs. NTg naïve 12m  $p < 0.001$ , 3xTg-AD re-test 16m vs. NTg re-test 16m  $p = 0.033$ , 3xTg-AD naïve 12m vs. 3xTg-AD naïve 16m  $p = 0.014$ ; Genotype differences, ANOVA,  $F(1,78) = 17.675$ ,  $p < 0.001$ . T6, Genotype differences, ANOVA,  $F(1,78) = 6.282$ ,  $p = 0.014$ .

#### Figure 5C.14

Males - Day 3: T1, ANOVA,  $F(5,74) = 3.075$ ,  $p = 0.014$ ; Genotype differences, ANOVA,  $F(1,78) = 6.477$ ,  $p = 0.013$ ; Re-test differences, ANOVA,  $F(1,78) = 6.616$ ,  $p = 0.012$ . T4, ANOVA,  $F(5,74) = 2.617$ ,  $p = 0.031$ , *post hoc* 3xTg-AD naïve 12m vs. NTg naïve 12m  $p = 0.026$ . T5, Genotype differences, ANOVA,  $F(1,78) = 5.066$ ,  $p = 0.027$ .

#### Figure 5C.15

Females - Day 1: T1, ANOVA,  $F(4,56) = 3.996$ ,  $p = 0.006$ , *post hoc* NTg naïve 12m vs. NTg re-test 16m  $p = 0.045$ . T2, ANOVA,  $F(4,56) = 4.477$ ,  $p = 0.003$ , *post hoc* NTg naïve 12m vs. NTg re-test 16m  $p = 0.015$ . T4, ANOVA,  $F(4,56) = 3.729$ ,  $p = 0.009$ , *post hoc* NTg naïve 12m vs. re-test NTg 16m  $p = 0.026$ . T5, ANOVA,  $F(4,56) = 2.809$ ,  $p = 0.034$ . T6, ANOVA,  $F(4,56) = 4.909$ ,  $p = 0.002$ , *post hoc* NTg naïve 12m vs. NTg re-test 16m  $p = 0.008$ .

#### Figure 5C.16

Females - Day 2: T1, ANOVA,  $F(4,56) = 2.588$ ,  $p = 0.046$ , *post hoc* 3xTg-AD naïve 12m vs. 3xTg-AD re-test 16m  $p = 0.028$ . T3, ANOVA,  $F(4,56) = 3.272$ ,  $p = 0.018$ .

#### Figure 5C.17

Females - Day 3: T3, ANOVA,  $F(4,56) = 2.606$ ,  $p = 0.045$ . T4, ANOVA,  $F(4,56) = 2.988$ ,  $p = 0.026$ . T5, ANOVA,  $F(4,56) = 3.025$ ,  $p = 0.025$ , *post hoc* 3xTg-AD retest 16m vs. NTg re-test 16m  $p = 0.045$ . T6, ANOVA,  $F(4,56) = 2.731$ ,  $p = 0.038$ , see figure 5C.

#### Figure 5C.18

3xTg-AD - Day 1, T1, ANOVA,  $F(5,71) = 4.431$ ,  $p = 0.001$ , *post hoc* female re-test 16m vs. Male naïve 12m  $p = 0.002$ ; Re-test differences, ANOVA,  $F(1,76) = 16.401$ ,  $p < 0.001$ . T2, ANOVA,  $F(5,71) = 4.372$ ,  $p = 0.002$ , *post hoc* female re-test 16m vs. male naïve 12m  $p = 0.004$ , female re-test 16m vs. male naïve 16m  $p = 0.050$ ; Re-test differences, ANOVA,  $F(1,76) = 15.013$ ,  $p < 0.001$ . T3, ANOVA,  $F(5,71) = 4.144$ ,  $p = 0.002$ , *post hoc* female re-test 16m vs. male naïve 12m  $p = 0.002$ ; Re-test differences, ANOVA,  $F(1,76) = 11.434$ ,  $p = 0.001$ . T4, ANOVA,  $F(5,71) = 2.572$ ,  $p = 0.034$ , *post hoc* female re-test 16m vs. male naïve 12m  $p = 0.035$ ; Sex differences, ANOVA,  $F(1,76) = 5.752$ ,  $p = 0.019$ ; Re-test differences, ANOVA,  $F(1,76) = 5.725$ ,  $p = 0.019$ . T5, ANOVA,  $F(1,76) = 4.794$ ,  $p = 0.001$ , *post hoc* female re-test 16m vs. male naïve 12m  $p = 0.042$ ; Sex differences, ANOVA,  $F(1,76) = 5.952$ ,  $p = 0.017$ ; Re-test differences, ANOVA,  $F(1,76) = 13.912$ ,  $p < 0.001$ . T6, ANOVA,  $F(5,71) = 5.723$ ,  $p < 0.001$ , *post hoc* female re-test 16m vs. male naïve 12m  $p < 0.001$ ; Sex differences, ANOVA,  $F(1,76) = 7.737$ ,  $p = 0.007$ ; Re-test differences, ANOVA,  $F(1,76) = 15.056$ ,  $p < 0.001$ .

#### Figure 5C.19

3xTg-AD - Day 2: T1, ANOVA,  $F(5,71) = 3.104$ ,  $p = 0.014$ , *post hoc* female re-test 16m vs. male naïve 12m  $p = 0.005$ ; Re-test differences, ANOVA,  $F(1,76) = 9.296$ ,  $p = 0.003$ . T2, Sex differences, ANOVA,  $F(1,76) = 6.607$ ,  $p = 0.012$ ; Re-test differences, ANOVA,  $F(1,76) = 4.183$ ,  $p = 0.044$ . T3, ANOVA,  $F(5,71) = 5.092$ ,  $p < 0.001$ , *post hoc* female re-test 16m vs. male naïve 12m  $p < 0.001$ , female re-test 16m vs. male re-test 16m  $p = 0.004$ ; Sex differences, ANOVA,  $F(1,76) = 16.280$ ,  $p < 0.001$ ; Re-test differences, ANOVA,  $F(1,76) = 4.017$ ,  $p = 0.049$ ; Sex differences, ANOVA,  $F(1,76) = 4.912$ ,  $p = 0.030$ . T4, ANOVA,  $F(5,71) = 4.043$ ,  $p = 0.003$ , *post hoc* female re-test 16m vs. male naïve 12m  $p = 0.001$ ; Sex differences, ANOVA,  $F(1,76) = 13.637$ ,  $p < 0.001$ . T5, ANOVA,  $F(5,71) = 5.511$ ,  $p < 0.001$ , *post hoc* female naïve 12m vs. male naïve 12m  $p = 0.015$ ; Sex differences, ANOVA,  $F(1,76) = 13.849$ ,  $p < 0.001$ . T6, ANOVA,  $F(5,71) = 3.529$ ,  $p = 0.007$ ; Sex differences, ANOVA,  $F(1,76) = 13.549$ ,  $p < 0.001$ .

#### Figure 5C.20

3xTg-AD - Day 3: T1, Sex differences, ANOVA,  $F(1,76) = 6.160$ ,  $p = 0.015$ . T2, ANOVA,  $F(1,76) = 6.384$ ,  $p = 0.014$ . T3, ANOVA,  $F(5,71) = 3.942$ ,  $p = 0.003$ , *post hoc* female naïve 12m vs. male naïve 12m  $p = 0.048$ , female re-test 16m vs. male naïve 12m  $p = 0.007$ ; Sex differences, ANOVA,  $F(1,76) = 13.021$ ,  $p = 0.001$ . T4, ANOVA,  $F(5,71) = 3.789$ ,  $p = 0.004$ , *post hoc* female naïve 12m vs. male naïve 12m  $p = 0.045$ , female re-test 16m vs. male naïve 12m  $p = 0.004$ ; Sex differences, ANOVA,  $F(1,76) = 10.172$ ,  $p = 0.002$ . T5, ANOVA,  $F(5,71) = 5.281$ ,  $p < 0.001$ , *post hoc* female naïve 12m vs. male naïve 12m  $p = 0.011$ , female re-test 16m vs. male naïve 12m  $p = 0.012$ ; Sex differences, ANOVA,  $F(1,76) = 18.229$ ,  $p < 0.001$ . T6, ANOVA,  $F(5,71) = 3.822$ ,  $p = 0.004$ , *post hoc* female re-test 16m vs. male naïve 12m  $p = 0.003$ ; Sex differences, ANOVA,  $F(1,76) = 14.803$ ,  $p < 0.001$ .