Serial Reversal in 3xTg-AD Mice

Kyle M Roddick[1], Heather M Schellinck[1], and Richard E Brown[1]

[1]*Department of Psychology and Neuroscience, Dalhousie University*

January 19, 2023

Subjects

Due to the small number of male mice, sexes are lumped together in this analysis. There are 33 mice included in this study. The 3xTg-AD mice (283 ± 118 days) were significantly younger than the B6129 mice (409 ± 197 days; t_{28} = -2.3, p = 0.0304; Table 1).

Training

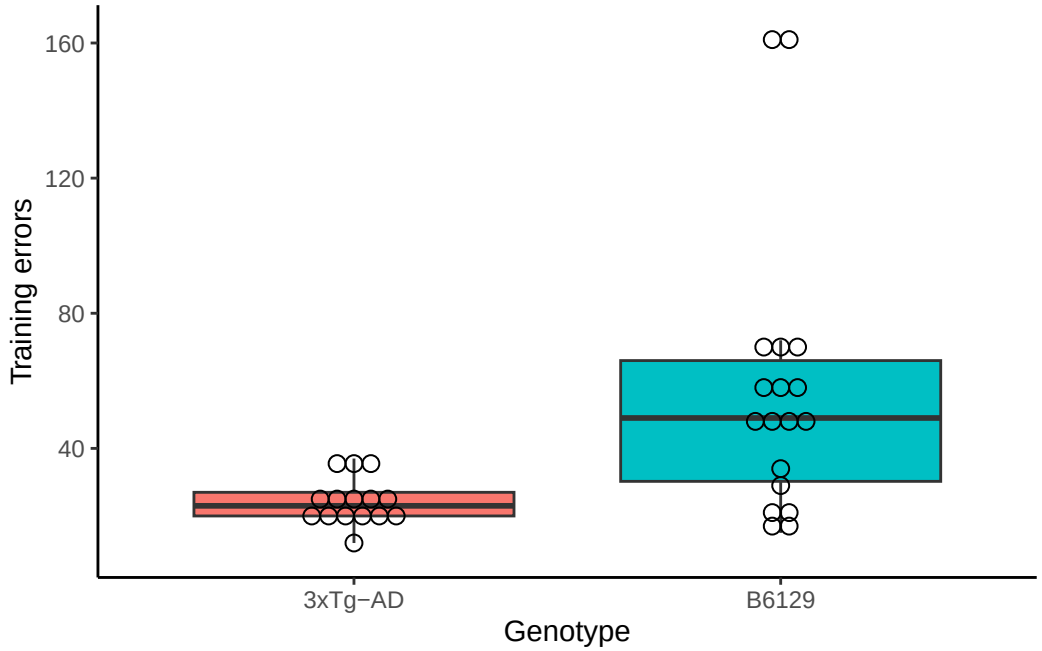

Figure 1: Errors made during training.

Table 1: Demographics of mice tested.

Genotype	Sex	Mean age (days)	Age range	N
3xTg-AD	Female	276.71	154 - 558	14
3xTg-AD	Male	366.00	366 - 366	1
B6129	Female	403.00	172 - 756	13
B6129	Male	425.40	298 - 635	5

An ANCOVA with age as a covariate was used to compare the number of errors made during training. The B6129 mice (58 ± 42) made more errors than the 3xTg-AD mice (58 ± 42; $F_{(1,30)} = 9.8$, $p = 0.004$, $\eta^2_G = 0.25$, Figure 1).

Difference scores

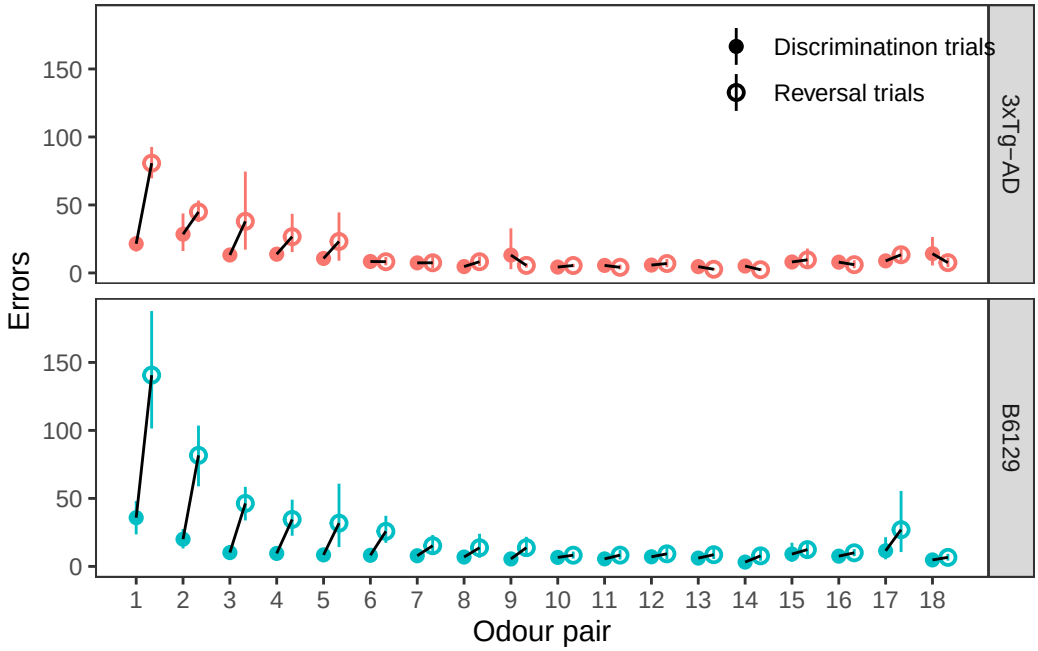

Figure 2: Errors (±95% CI) made by the mice at on each odour pair.

The sequence of odour pairs was divided into thirds, and ANCOVAs, with age as the covariate, examining the differences between the errors on the discrimination trials and the reversal trials were run on each third. Greenhouse-Geisser corrections were applied when Mauchly's test for sphericity detected that within-subjects factors violated sphericity.

In the first third of odour pairs (1 - 6), there were significant effects of genotype ($F_{(1,22)} = 15$, $p < 0.001$, $\eta^2_G = 0.094$), with the B6129 mice (44.52885 ± 63.51423) having greater differences scores than the 3xTg-AD mice (19.54762 ± 40.96852). There was no significant effect of odour pair ($F_{(2.3,50)} = 1.4$, $p = 0.25$, $\eta^2_G = 0.051$; Figure 2), nor a significant interaction ($F_{(2.3,50)} = 0.68$, $p = 0.53$, $\eta^2_G = 0.025$).

On the second third of odour pairs (7 - 12) there were no significant effects (p's >= 0.12).

On the last third of odour pairs (13 - 18) there was a significant interaction between age and odour pair ($F_{(2.2,55)} = 5.7$, $p = 0.004$, $\eta^2_G = 0.16$), but no significant effects of genotype ($F_{(1,25)} = 3.1$, $p = 0.09$, $\eta^2_G = 0.02$), odour pair ($F_{(2.2,55)} = 2.5$, $p = 0.09$, $\eta^2_G = 0.076$), nor an interaction between genotype and odour pair ($F_{(2.2,55)} = 0.34$, $p = 0.73$, $\eta^2_G = 0.011$).

Discrimination

The sequence of odour pairs was divided into thirds, and ANCOVAs, with age as the covariate, examining the errors on the discrimination trials were run on each third (Figure 3). Greenhouse-Geisser corrections were applied when Mauchly's test for sphericity detected that within-subjects factors violated sphericity.

There were no significant effects in the first (1 - 6), second (7 - 12) or last thirds (13 - 18) of trials (p's >= 0.058).

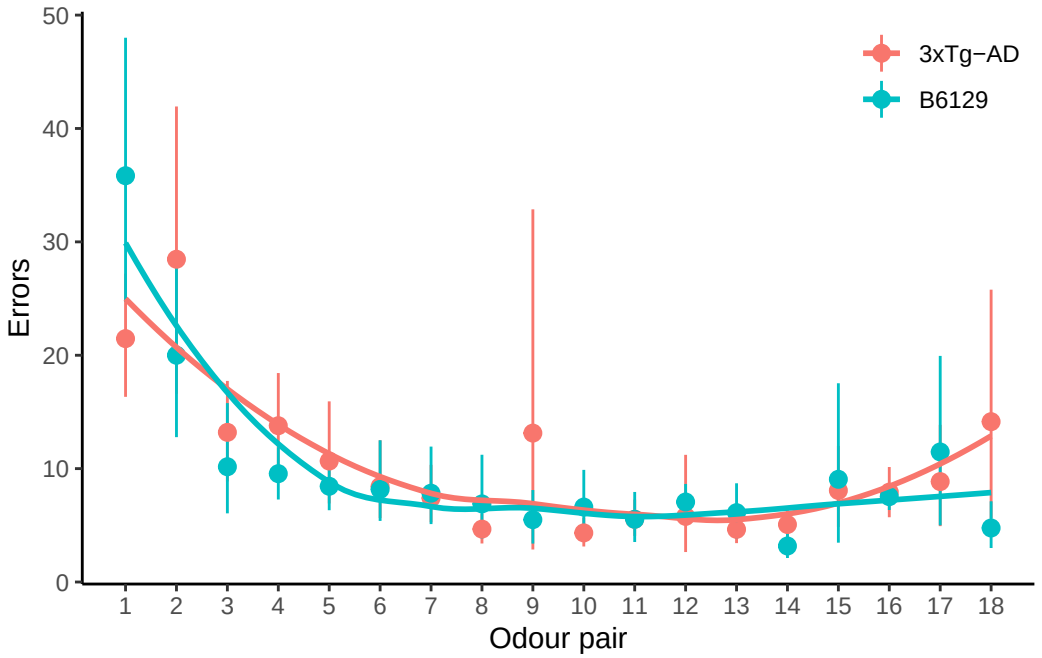

Figure 3: Errors (±95% CI) made by the mice at on each odour pair during the discrimination stages.

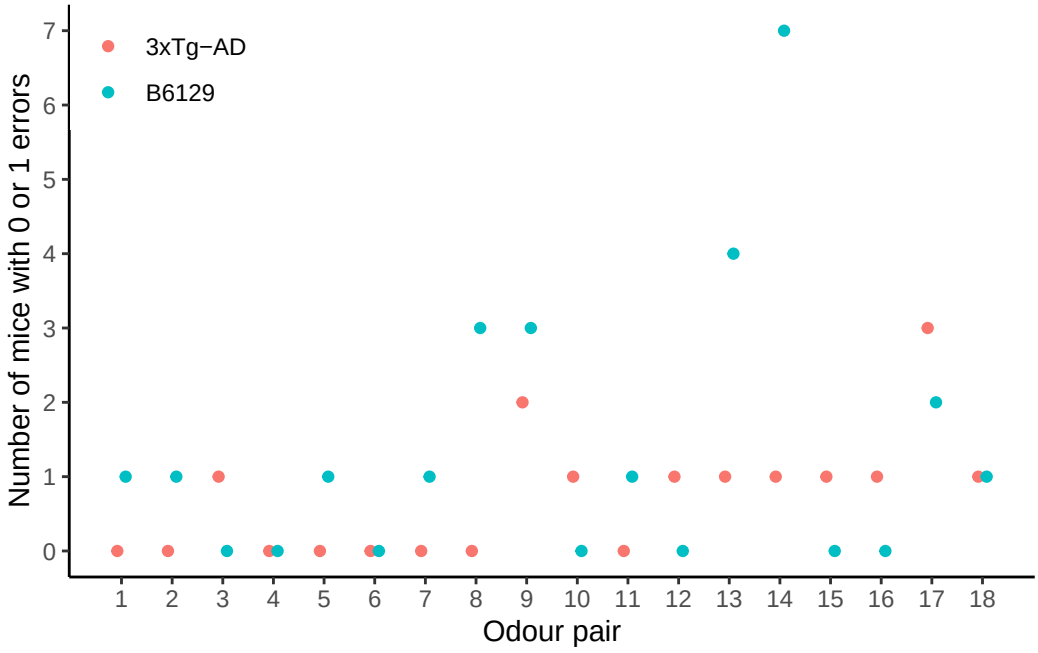

Figure 4: Number of mice showing errorless learning on each odour pair during discrimination.

Near errorless learning

There were 35 times where mice made a single error on the initial discrimination of the odour pair, and 3 times where a mouse made zero errors (Figure 4). With 21 different mice passing at least one discrimination with just one or zero errors. One mouse, a B6129, had one or fewer errors on the initial discrimination of 6 odour pairs.

Pearson's χ^2 tests with Yate's continuity corrections were run on the number of mice showing errorless learning. The χ^2 on the effect of odour pair was significant ($\chi^2_{17} = 43$, $p < 0.001$), while the χ^2 on the effect of genotype was not ($\chi^2_1 = 1.5$, $p = 0.214$).

Age effects

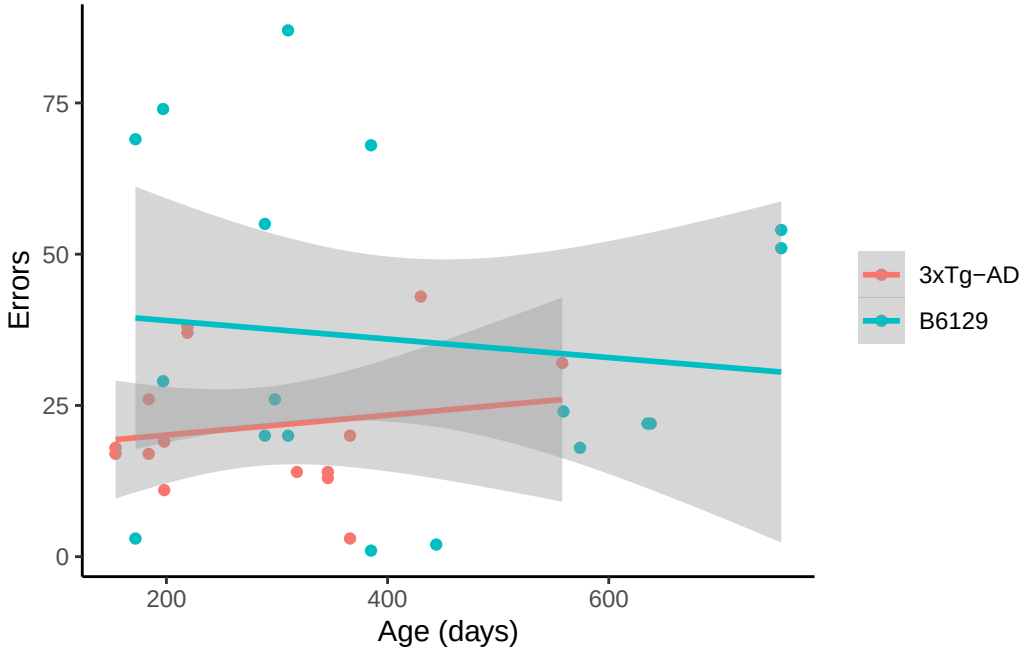

Figure 5: Correlation between age and errors made on odour pair one discrimination.

Pearson's correlations were used to compare the number of errors made on odour pair one to the age of the mice for each genotype (Figure 5). The correlations were not significant for either the B6129 (r = -0.11, p = 0.655), nor the 3xTg-AD (r = 0.17, p = 0.543) mice, thus there was no significant change in errors with age.

Reversal

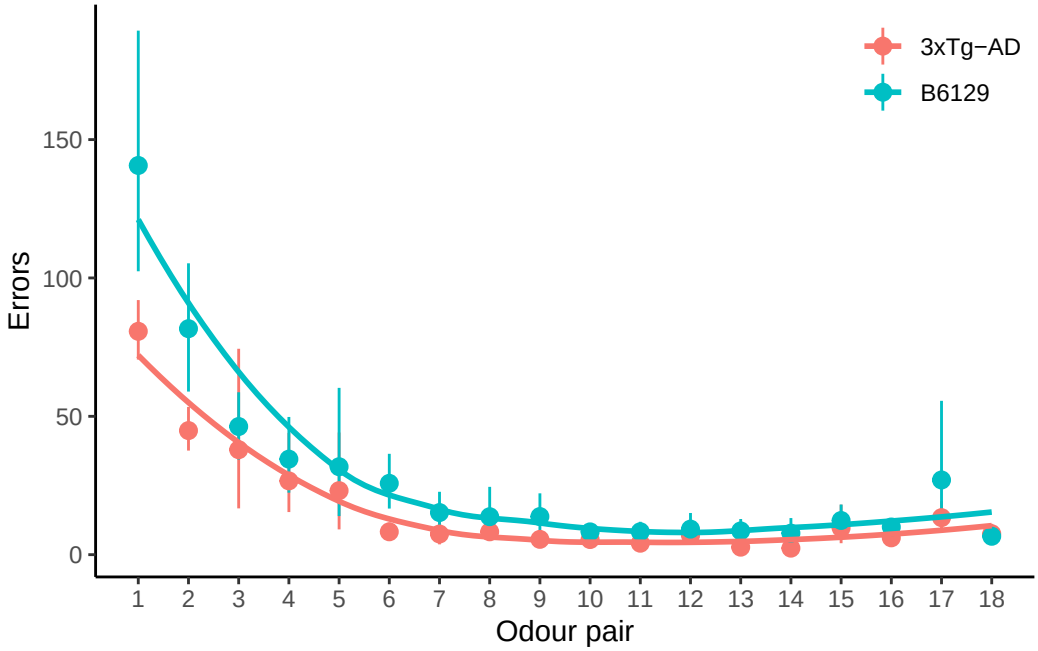

Figure 6: Errors (±95% CI) made by the mice at on each odour pair during the reversal stages.

The sequence of odour pairs was divided into thirds, and ANCOVAs, with age as the covariate, examining the errors on the reversal trials were run on each third (Figure 6). Greenhouse-Geisser corrections were applied when Mauchly's test for sphericity detected that within-subjects factors violated sphericity.

In the first third (1 - 6) of odour pairs there were significant effects of genotype ($F_{(1,23)} = 8.2$, $p = 0.009$, $\eta^2_G = 0.057$), with the B6129 mice (60 ± 67) making more errors than the 3xTg-AD mice (36 ± 41). but no significant effect of odour pair ($F_{(2.6,59)} = 1.3$, $p = 0.27$, $\eta^2_G = 0.046$), nor an interaction ($F_{(2.6,59)} = 1.1$, $p = 0.34$, $\eta^2_G = 0.039$).

There were no significant effects in the second (7 - 12) of odour pairs (p's >= 0.007).

In the last third (13 - 18) of odour pairs there was a significant interaction between age and odour pair ($F_{(1.4,36)} = 6.7$, $p = 0.007$, $\eta^2_G = 0.18$), but no main effects of genotype ($F_{(1,25)} = 0.8$, $p = 0.38$, $\eta^2_G = 0.006$), odour pair ($F_{(1.4,36)} = 2.8$, $p = 0.09$, $\eta^2_G = 0.082$), nor an interaction between the two ($F_{(1.4,36)} = 0.13$, $p = 0.81$, $\eta^2_G = 0.004$).

Near errorless learning

There were 30 instances of mice making a single error on the reversal of the odour pair, and 8 instances of a mouse making zero errors (Figure 7). With 18 mice passing at least one reversal with just one or zero errors. One mouse, a 3xTg-AD, had one or fewer errors on the reversal of 5 odour pairs.

Pearson's χ^2 tests with Yate's continuity corrections were run on the number of mice showing errorsless learning. The χ^2 on the effect of odour pair was significant (${\chi^2}_{17} = 49$, $p < 0.0001$), as was the χ^2 on the effect of genotype (${\chi^2}_1 = 4.6$, $p = 0.0323$), with the 3xTg-AD mice having more errorless reversals than the B6129 mice.

Age effects

Pearson's correlations were used to compare the number of errors made on odour pair one to the age of the mice for each genotype. The correlations were not significant for either the B6129 ($r = 0.23$, $p = 0.372$), nor the 3xTg-AD ($r = 0.12$, $p = 0.689$) mice (Figure 8).

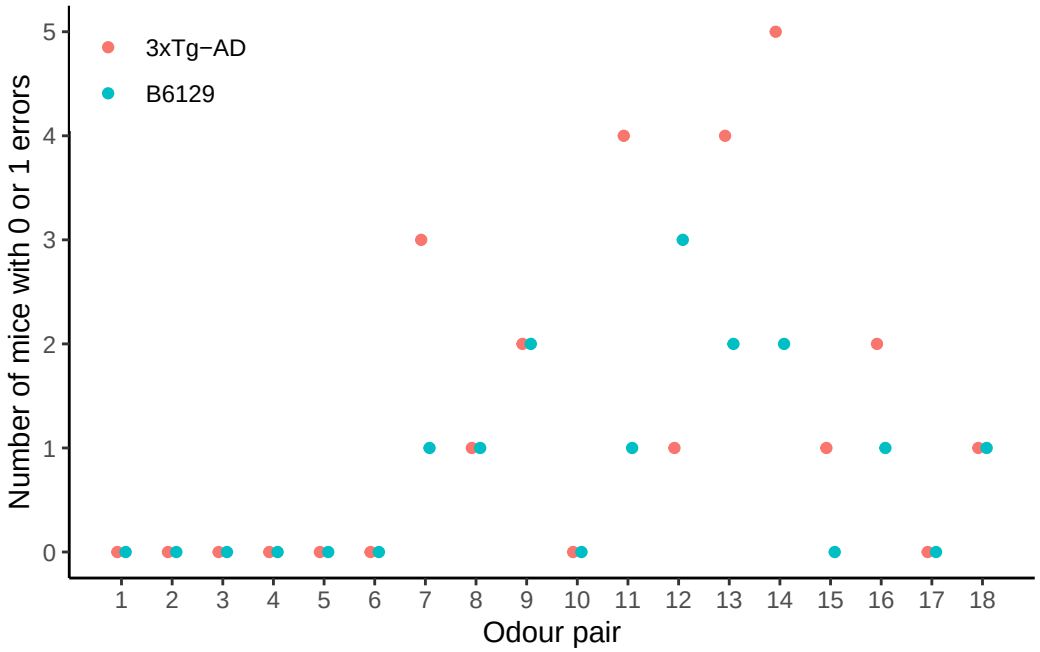

Figure 7: Number of mice showing errorless learning on each odour pair during reversal

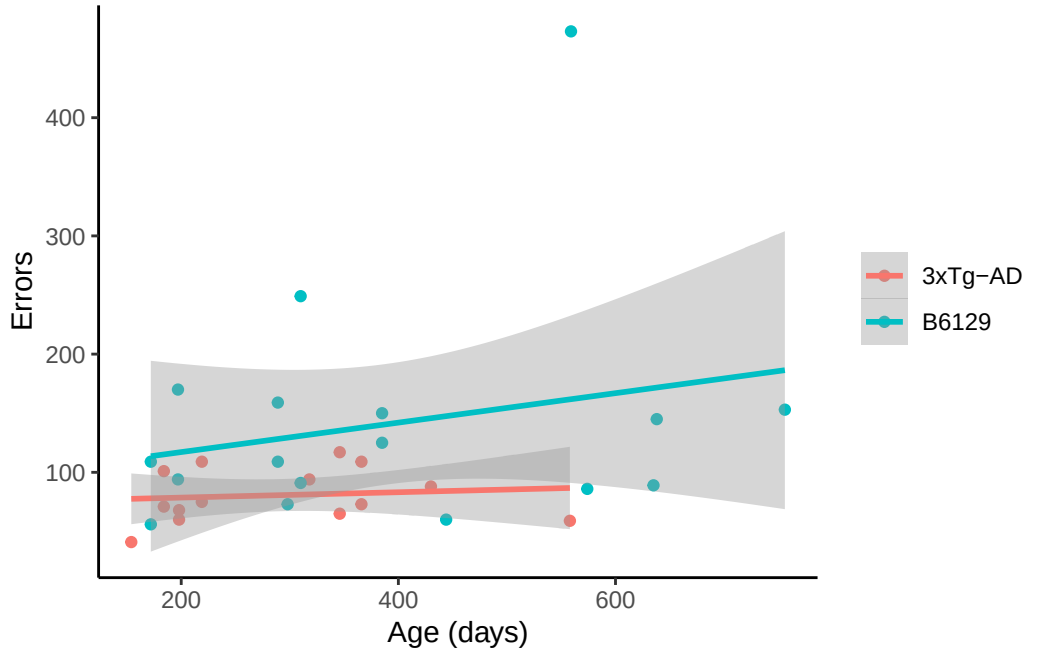

Figure 8: Correlation between age and errors made on odour pair one reversal.

Total errors

An ANCOVA, with age as the covariate, was used to assess the total errors made during the discrimination and reversal trials. There was a significant effect of genotype ($F_{(1,30)} = 6.5$, $p = 0.016$, $\eta^2_G = 0.18$; Figure 9).

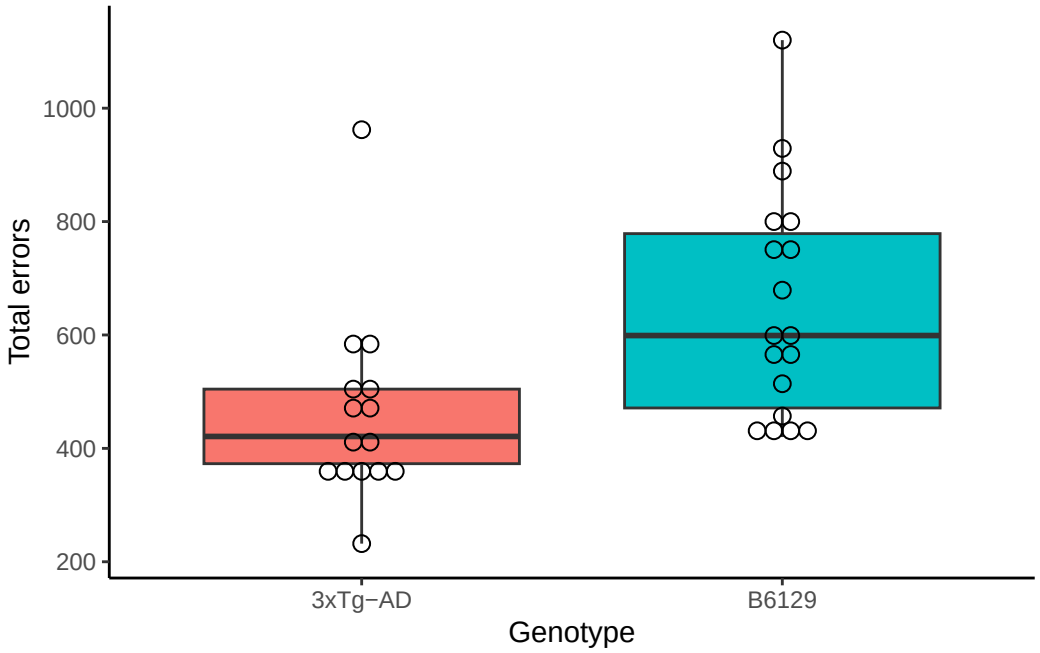

Figure 9: Total errors made, excluding retest.

Age effects

Pearson correlations were used to compare the total number of errors made to the age of the mice for each genotype (Figure 10). The correlations were not significant for either the B6129 ($r = 0.1$, $p = 0.692$), nor the 3xTg-AD ($r = -0.098$, $p = 0.727$) mice.

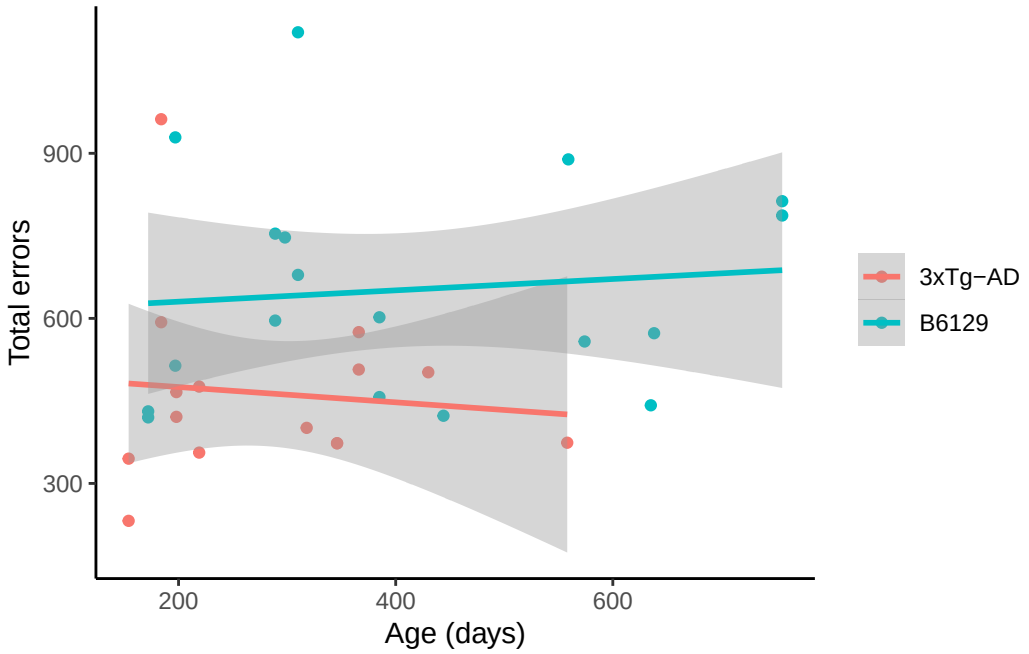

Figure 10: Correlation between age and total errors made.

Retest

Due to mice dying, only 15 B6129 and 9 3xTg-AD mice were given the retest.

The retest occurred between 30 and 94 days after the final reversal. There was no difference between between the days until the retest for the B6129 (55 ± 24) and 3xTg-AD (75 ± 23; $t_{18} = 2$, $p = 0.062$).

An ANCOVA, with age as the covariate, was used to assess the number of errors made during the retest. There was no significant effect of genotype ($F_{(1,21)} = 1.3$, $p = 0.26$, $\eta^2_G = 0.06$; Figure 11)

A paired t-test was used to compare the number of errors made during the retest to the numbers of errors made on the final odour discrimination. The mean number of errors made during the retest (40 ± 24) was significantly higher than the errors made on the final odour discrimination (6.8 ± 8.4; $t_{23} = 8.3$, $p < 0.0001$).

Age effects

Pearson correlations were used to compare the number of errors made on the retest to the age of the mice for each genotype (Figure 12). The correlations was not significant for the B6129 ($r = 0.34$, $p = 0.214$), but was for the 3xTg-AD ($r = -0.67$, $p = 0.05$) mice.

Time from last test effect

Pearson correlations were used to compare the number of errors made on the retest to the days since the final reversal. There was a significant, positive correlation for the B6129 mice ($r = 0.62$, $p = 0.013$), but not for the 3xTg-AD mice ($r = 0.4$, $p = 0.286$; Figure 13).

An ANCOVA, with age as a covariate, was run examining the effects of genotype and time since last reversal on the errors made on the retest. The time since last reversal was binned into 30, 60, and 90 day groups. There were no significant effects (p's >= 0.14).

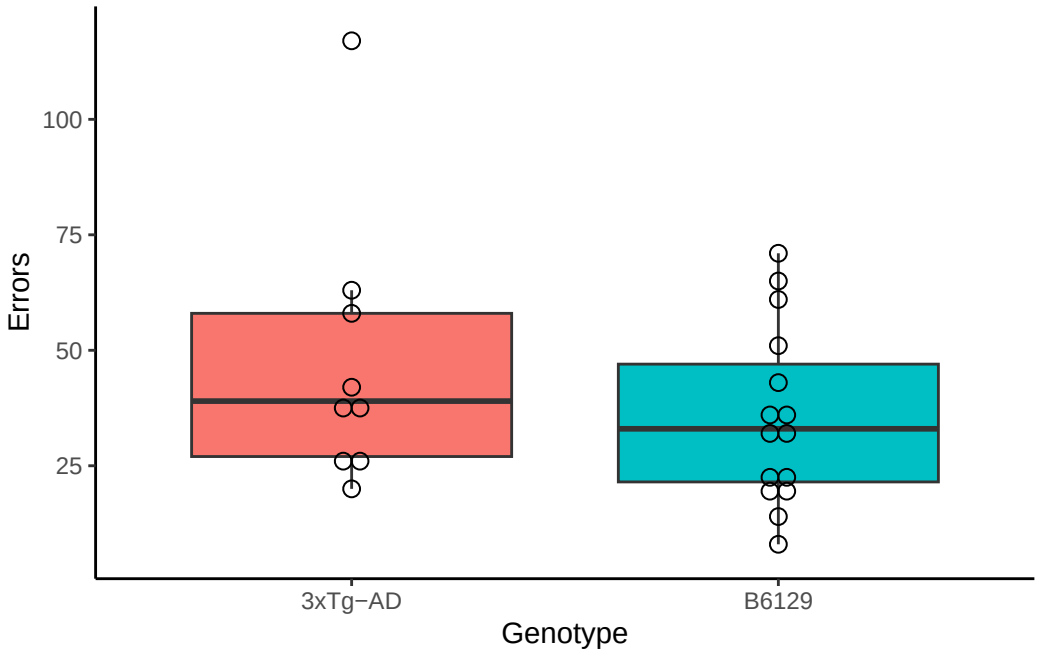

Figure 11: Total errors made during retest.

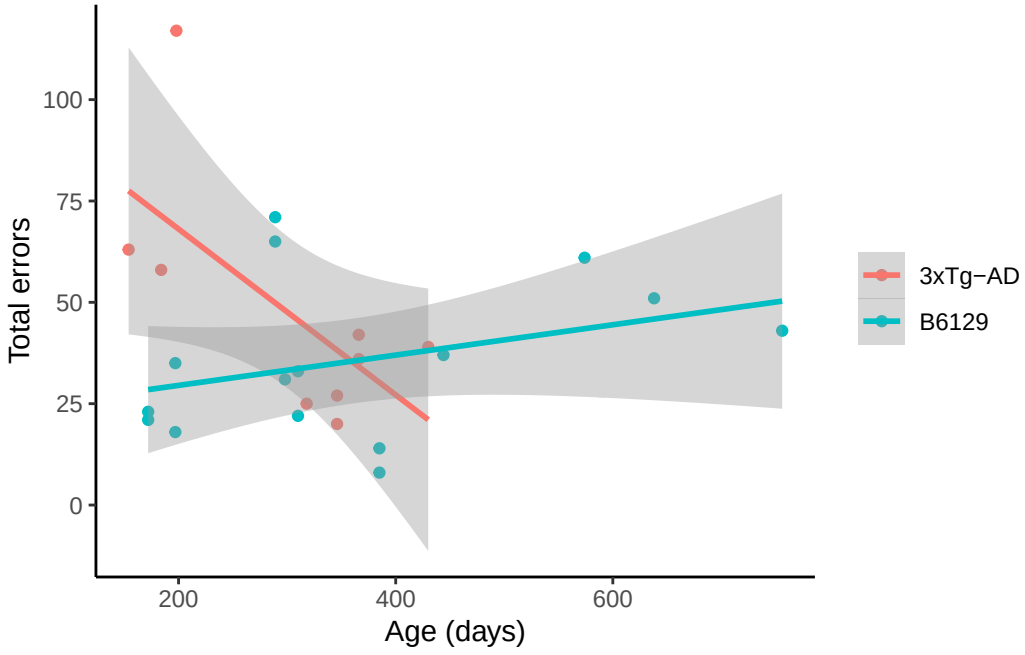

Figure 12: Correlation between age and errors made on the retest.

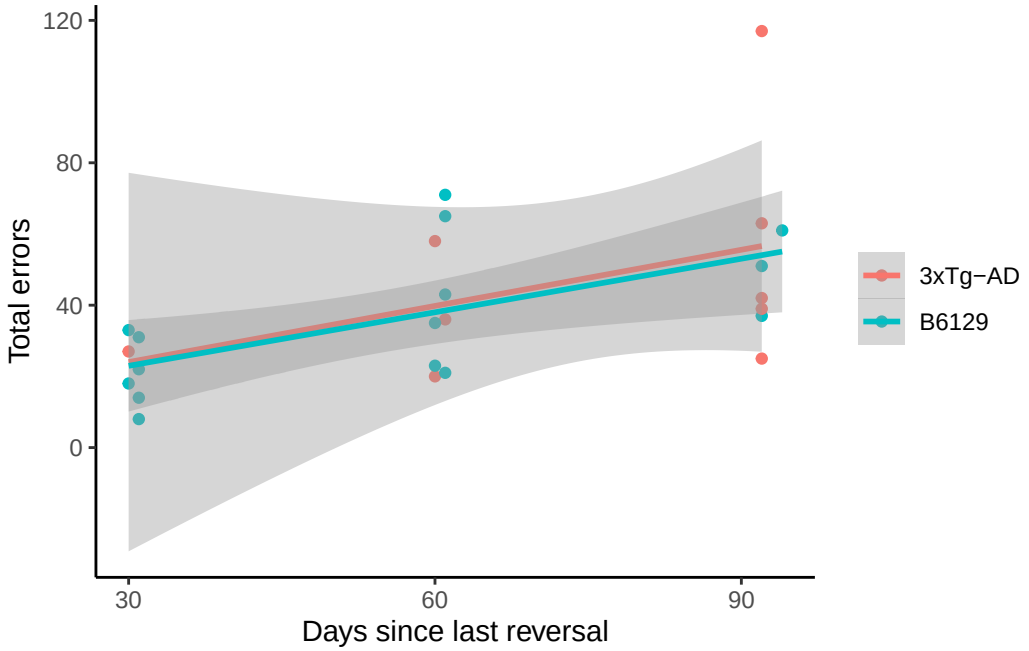

Figure 13: Correlation between days after last reversal and errors made on the retest.