

Table S1

Gene	Sequences	
MCP-1	Forward	AGCTGTAGTTTTTGTACCAAGC
	Reverse	GACCTTAGGGCAGATGCAGT
TNF- α	Forward	CCCCAGTCTGTATCCTTCT
	Reverse	ACTGTCCCAGCATCTTGT
IL-1 β	Forward	GATGAAGGGCTGCTTCCAAAC
	Reverse	TCCACAGCCACAATGAGTGA
IL-6	Forward	TTCACAAGTCCGGAGAGGAG
	Reverse	TCCACGATTTCCCAGAGAAC
IL-10	Forward	CCAAGCCTTATCGGAAATGA
	Reverse	TTCTCACCCAGGGAATTCAA
GAPDH	Forward	ATTCAACGGCACAGTCAA
	Reverse	CTCGCTCCTGGAAGATGG
16S rRNA	Forward	CGCTAGTAATCGTGGATCAGAATG
	Reverse	TGTGACGGGCGGTGTGTA

Table S1 List of primer sequences used in this study.

Figure S1

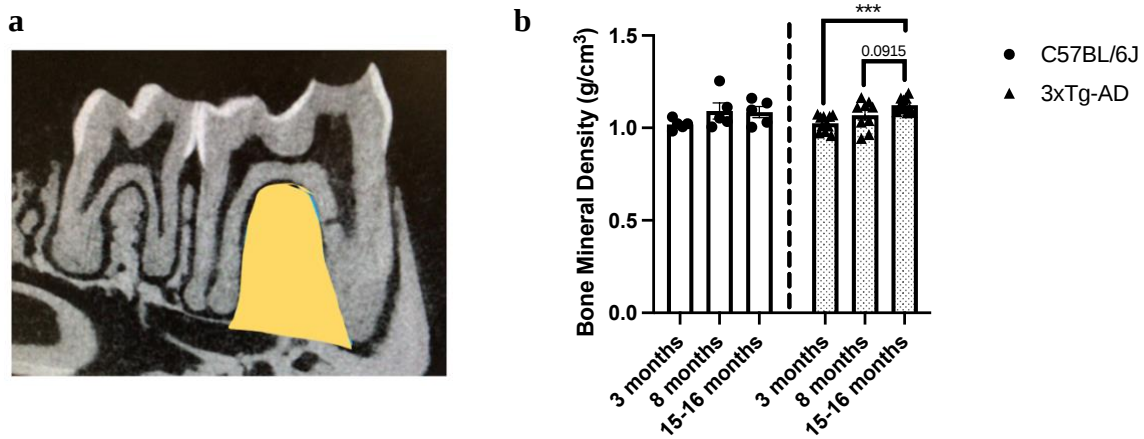


Fig. S1 Assessment of bone mineral density from the right mandibular jaws of C57BL/6J and 3×Tg-AD mice at 3 months, 8 months, and 15-16 months of age. (a) A representative two-dimensional sagittal image of a right mandibular jaw depicting the region of interest (highlighted in yellow) for the quantitative measurement of bone mineral density. **(b)** Quantitative analysis of bone mineral density. Data are presented as mean ± SEM (C57BL/6J mice: n = 5/age group, 3×Tg-AD mice: n = 9-11/age group). Statistical analysis was done using one-way ANOVA with Tukey's post-hoc test. *** $p < 0.001$

Figure S2

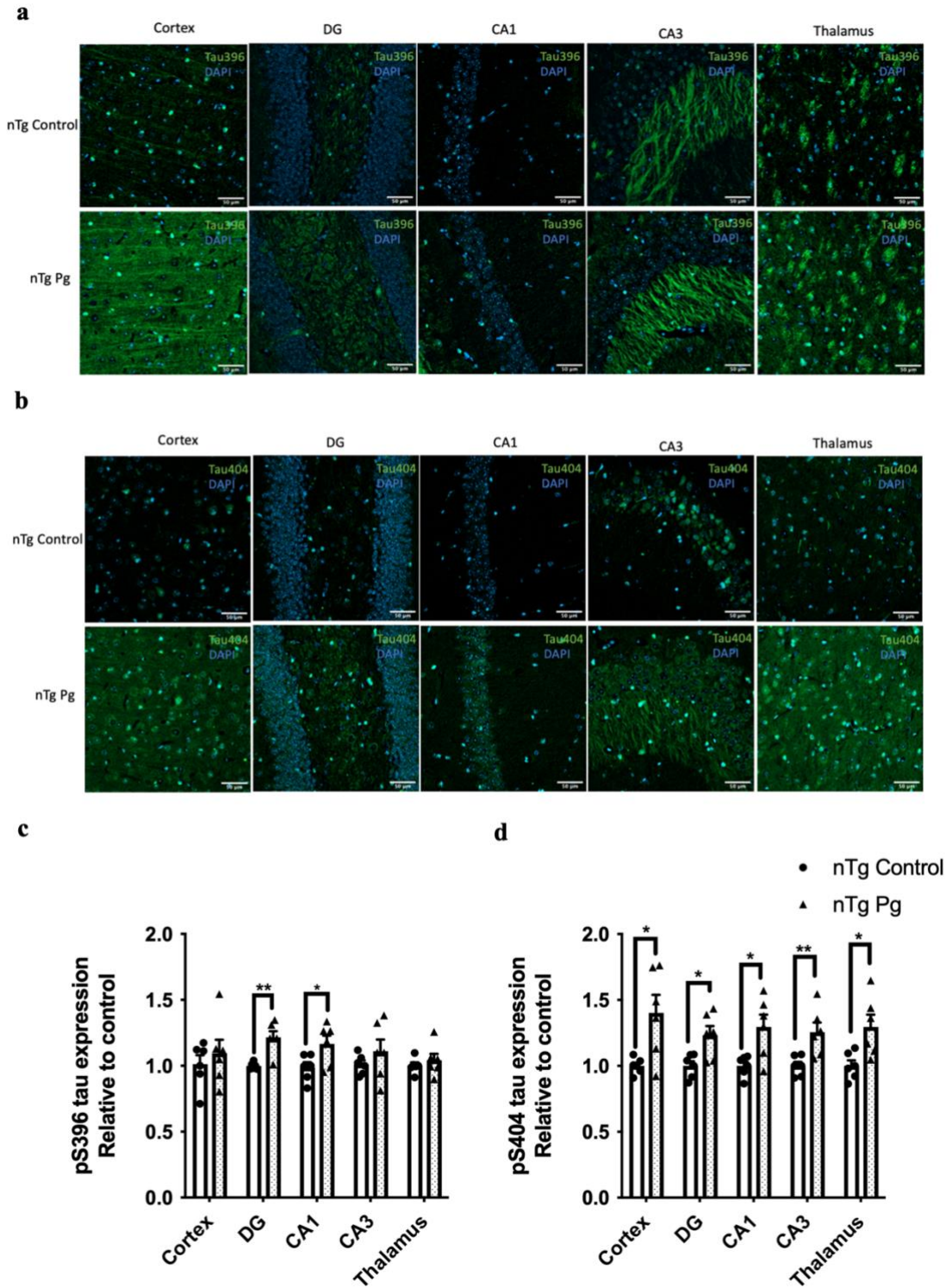


Fig. S2 Periodontitis induced by the injection of heat-killed *Porphyromonas gingivalis* resulted in increased phosphorylated tau proteins immunoreactivity in the brains of non-transgenic (nTg) mice.

(a) Representative images of immunofluorescence staining for phosphorylated tau Ser396 (green) and DAPI (blue) in the cortex, sub-regions of the hippocampus, and thalamus of nTg mice in each group. **(b)** Representative images of immunofluorescence staining for phosphorylated tau Ser404 (green) and DAPI (blue) in the cortex, sub-regions of the hippocampus, and thalamus of nTg mice in each group. **(c, d)** Quantification of (c) phosphorylated tau Ser396 and (d) phosphorylated tau Ser404 immunofluorescence intensity in the cortex, sub-regions of the hippocampus, and thalamus of nTg mice in each group. Data are presented as mean $\pm$ SEM (n = 6). Statistical analysis was done using unpaired t test. * $p < 0.05$, ** $p < 0.01$

Figure S3

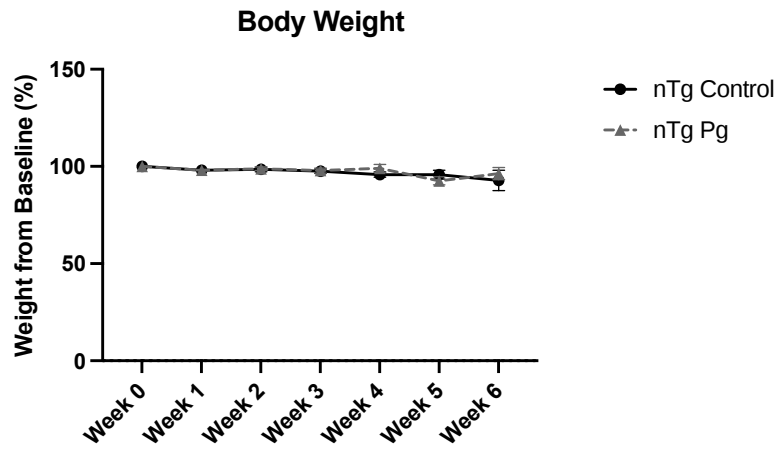


Fig. S3 Non-transgenic (nTg) mice body weight expressed as a percent change from baseline during the experimental period of heat-killed *Porphyromonas gingivalis* injections. Data are presented as mean $\pm$ SEM (n = 7-8). Statistical analysis was done using two-way ANOVA with Bonferroni's post-hoc test.

Figure S4

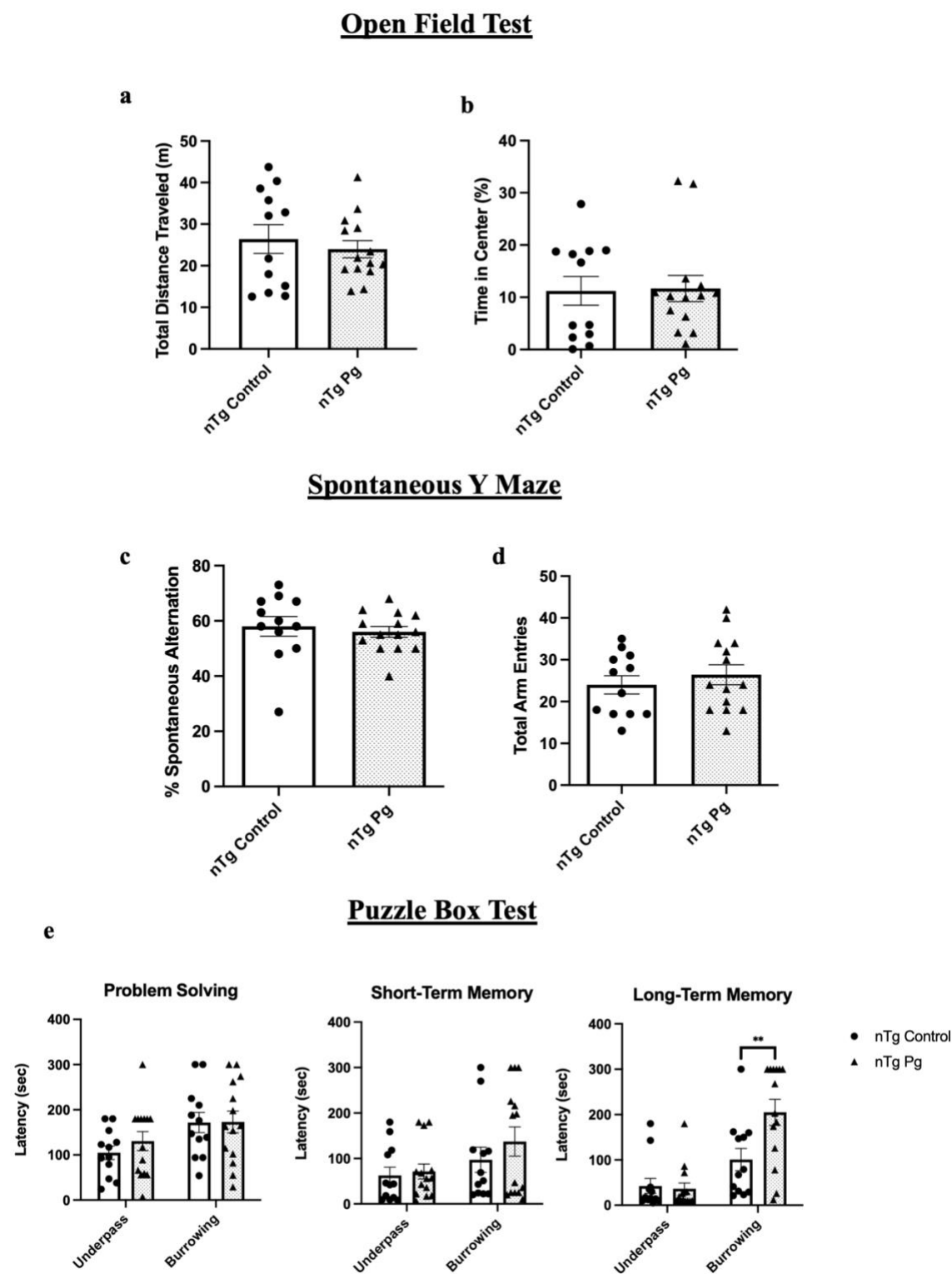


Fig. S4 Periodontitis induced by the injection of heat-killed *Pg* resulted in impairment of long-term memory in non-transgenic (nTg) mice. (a, b) Open field test for the assessment of general exploration and anxiety behavior. (a) Total distance traveled and (b) the percentage of time spent in center were examined. **(c, d)** Spontaneous Y maze test for the assessment of short-term spatial working memory. (c) Percentage spontaneous alternation and (d) the number of total arm entries were examined. **(e)** Puzzle box test for the assessment of problem-solving abilities and executive functions. Data are presented as mean $\pm$ SEM (n = 12-14). Statistical analysis was done using unpaired t test. **** $p < 0.01$**

Figure S5

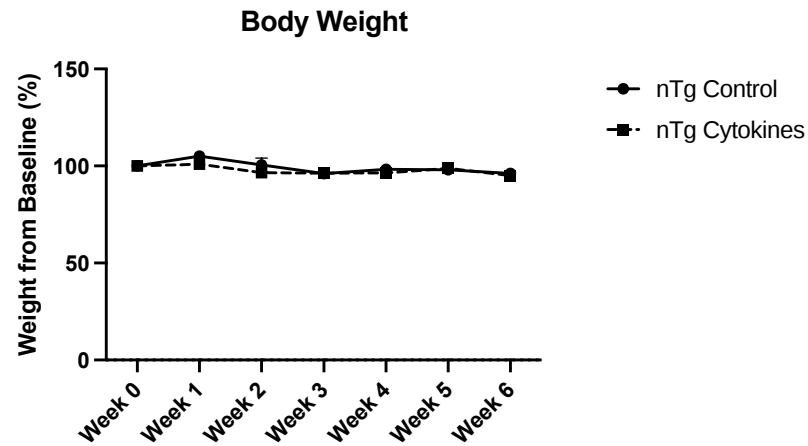


Fig. S5 Non-transgenic (nTg) mice body weight expressed as a percent change from baseline during the experimental period of mixed cytokines injections. Data are presented as mean $\pm$ SEM ($n = 7$). Statistical analysis was done using two-way ANOVA with Bonferroni's post-hoc test.

Figure S6

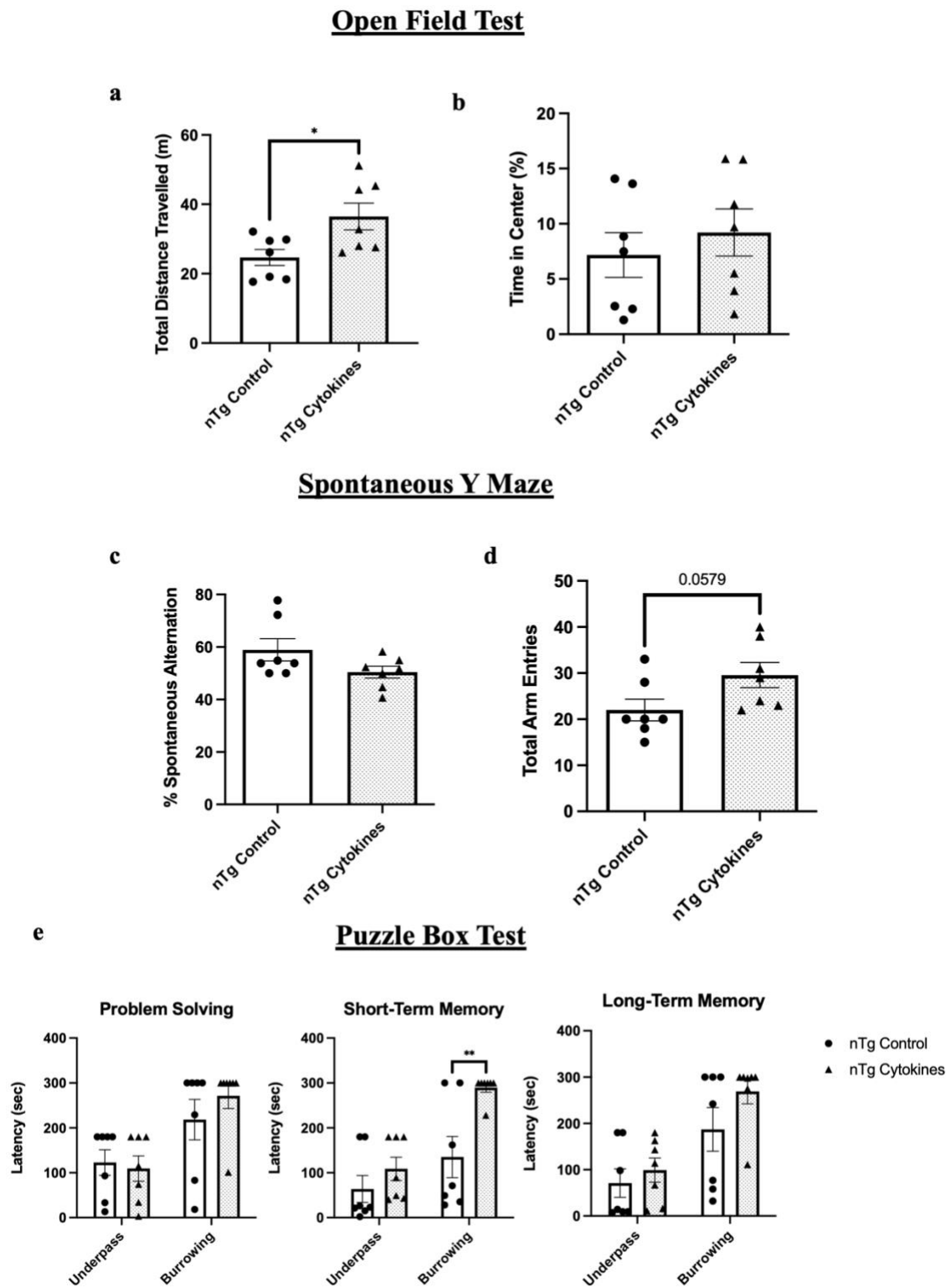


Fig. S6 Injections of mixed cytokines resulted in hyperactivity and impairment of short-term memory in non-transgenic (nTg) mice. (a, b) Open field test for the assessment of general exploration and anxiety behavior. (a) Total distance traveled and (b) the percentage of time spent in center were examined. **(c, d)** Spontaneous Y maze test for the assessment of short-term spatial working memory. (c) Percentage spontaneous alternation and (d) the number of total arm entries were examined. **(e)** Puzzle box test for the assessment of problem-solving abilities and executive functions. Data are presented as mean $\pm$ SEM (n = 7). Statistical analysis was done using unpaired t test. * $p < 0.05$, ** $p < 0.01$

Figure S7

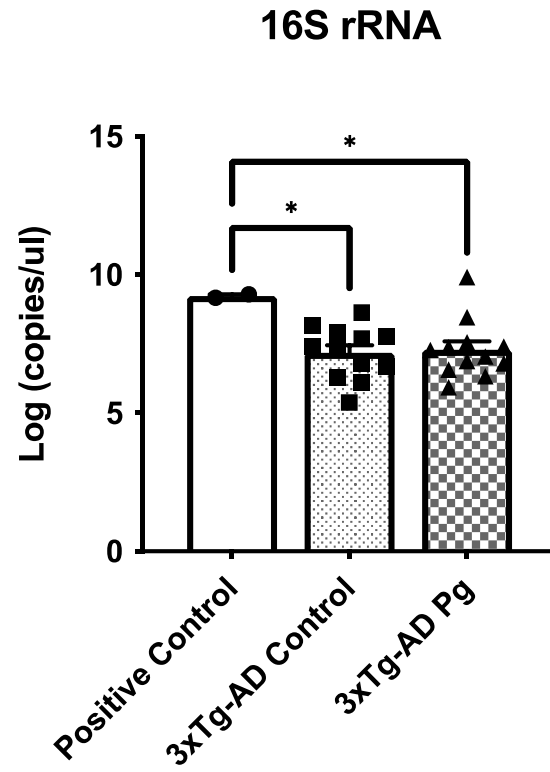


Fig. S7 Total bacterial load in the gums of 3×Tg-AD mice measured by 16S rRNA real-time PCR at the end of the experimental period. Tissue DNA spiked with 100 ng of Pg DNA was included as positive controls. Data are presented as mean ± SEM (n = 12). Statistical analysis was done using one-way ANOVA with Tukey's post-hoc test. * $p < 0.05$

Figure S8

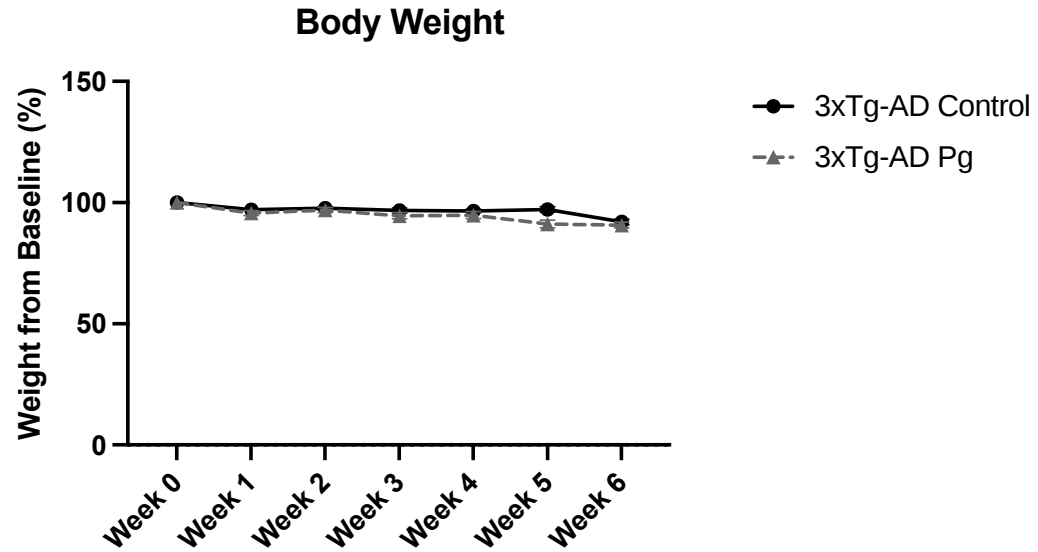


Fig. S8 3×Tg-AD mice body weight expressed as a percent change from baseline during the experimental period of heat-killed *Pg* injections. Data are presented as mean $\pm$ SEM (n = 7-8). Statistical analysis was done using two-way ANOVA with Bonferroni's *post-hoc* test.

Figure S9

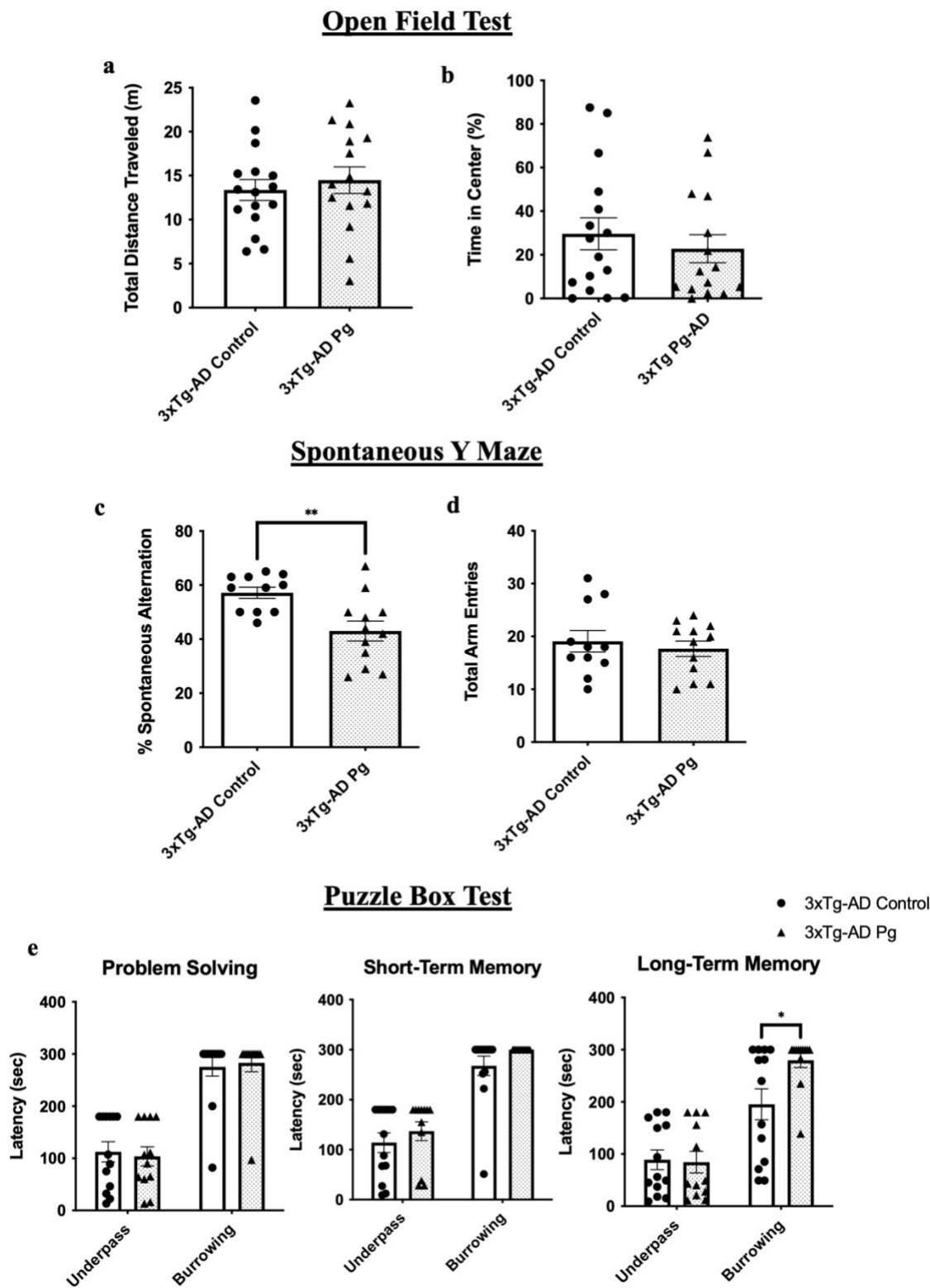


Fig. S9 Periodontitis induced by the injection of heat-killed *Porphyromonas gingivalis* resulted in impairment of both short- and long-term memory in 3×Tg-AD mice. (a, b) Open field test for the assessment of general exploration and anxiety behavior. (a) Total distance traveled and (b) the percentage of time spent in center were examined. Data are presented as mean $\pm$ SEM (n = 15-16). **(c, d)** Spontaneous Y maze test for the assessment of short-term spatial working memory. (c) Percentage spontaneous alternation and (d) the number of total arm entries were examined. Data are presented as mean $\pm$ SEM (n = 11-12). (e) Puzzle box test for the assessment of problem-solving abilities and executive functions. Data are presented as mean $\pm$ SEM (n = 12-13). Statistical analysis was done using unpaired t test. * $p < 0.05$, ** $p < 0.01$

Figure S10

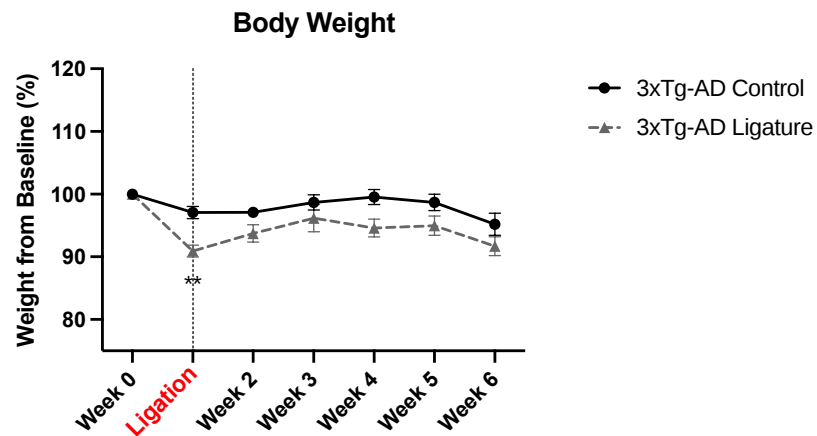


Fig. S10 3×Tg-AD mice body weight expressed as a percent change from baseline during the experimental period of ligature placement. Data are presented as mean ± SEM (n = 12). Statistical analysis was done using two-way ANOVA with Bonferroni's *post-hoc* test. ** $p < 0.01$

Figure S11

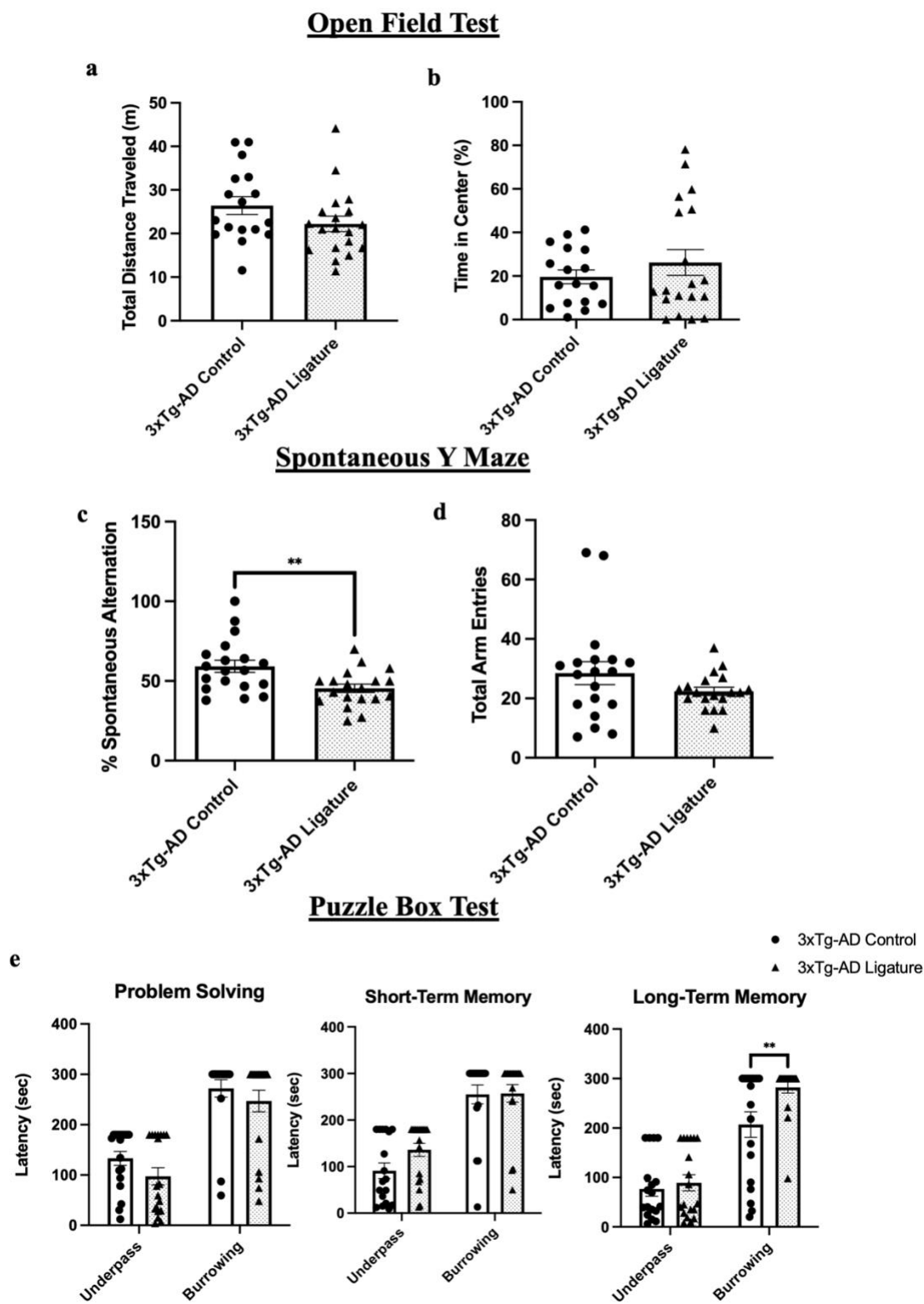


Fig. S11 Ligature-induced periodontitis resulted in impairment of both short- and long-term memory in 3×Tg-AD mice. (a, b) Open field test for the assessment of general exploration and anxiety behavior. (a) Total distance traveled and (b) the percentage of time spent in center were examined. Data are presented as mean $\pm$ SEM (n = 17-19). **(c, d)** Spontaneous Y maze test for the assessment of short-term spatial working memory. (c) Percentage spontaneous alternation and (d) the number of total arm entries were examined. Data are presented as mean $\pm$ SEM (n = 19). Data are presented as mean $\pm$ SEM (n = 18-19). Statistical analysis was done using unpaired t test. **** $p < 0.01$**

Figure S12

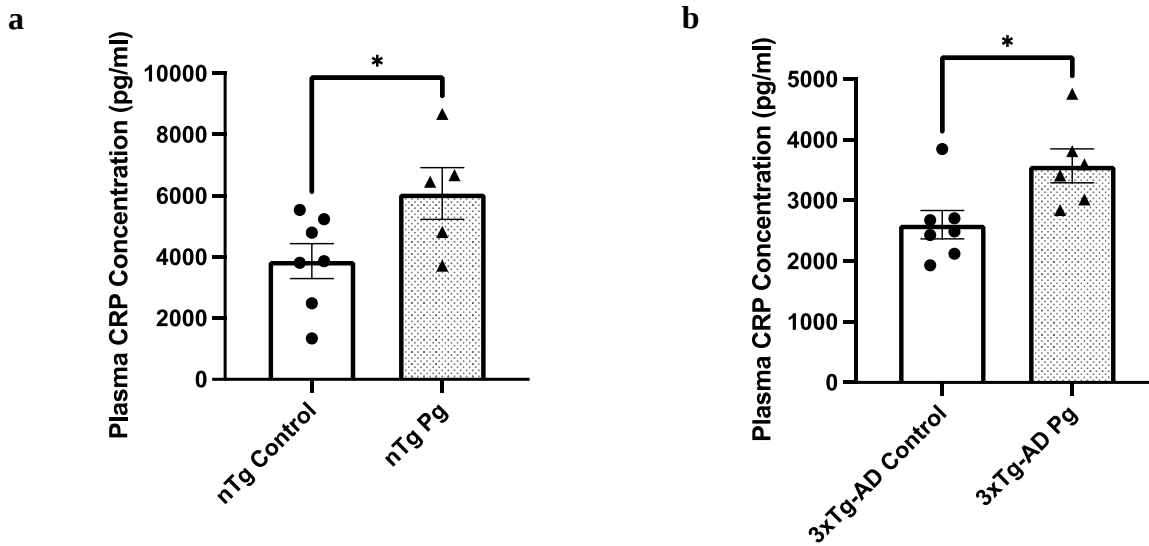


Fig. S12 Periodontitis induced by the injection of heat-killed *Porphyromonas gingivalis* resulted in elevated CRP levels in the plasma. (a) Plasma CRP concentration in nTg mice from each group. **(b)** Plasma CRP concentration in 3×Tg-AD mice from each group. Data are presented as mean $\pm$ SEM (n = 5-7). Statistical analysis was done using unpaired t test. *p < 0.05

Figure S13

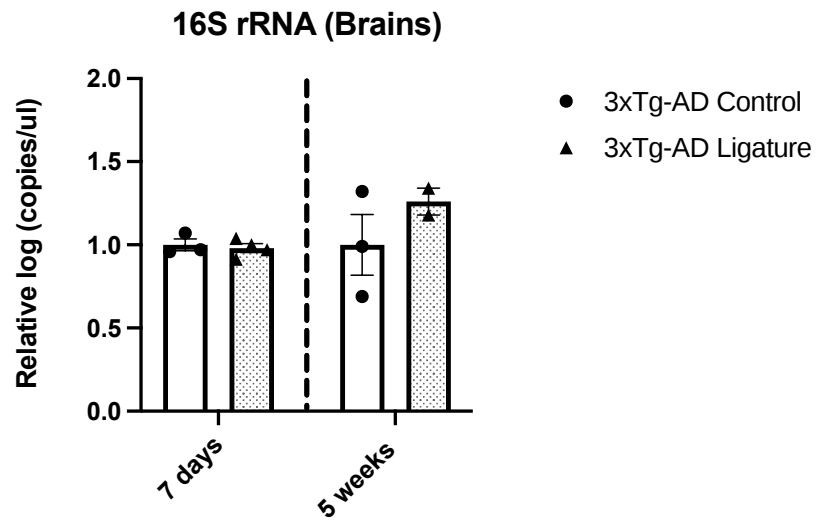


Fig. S13 Total bacterial load in the whole brain homogenates of 3×Tg-AD mice at 7-day and 5-weeks post-ligation measured by 16S rRNA real-time PCR. Data are presented as mean ± SEM (n = 2-4). Statistical analysis was done using unpaired t test.

Figure S14

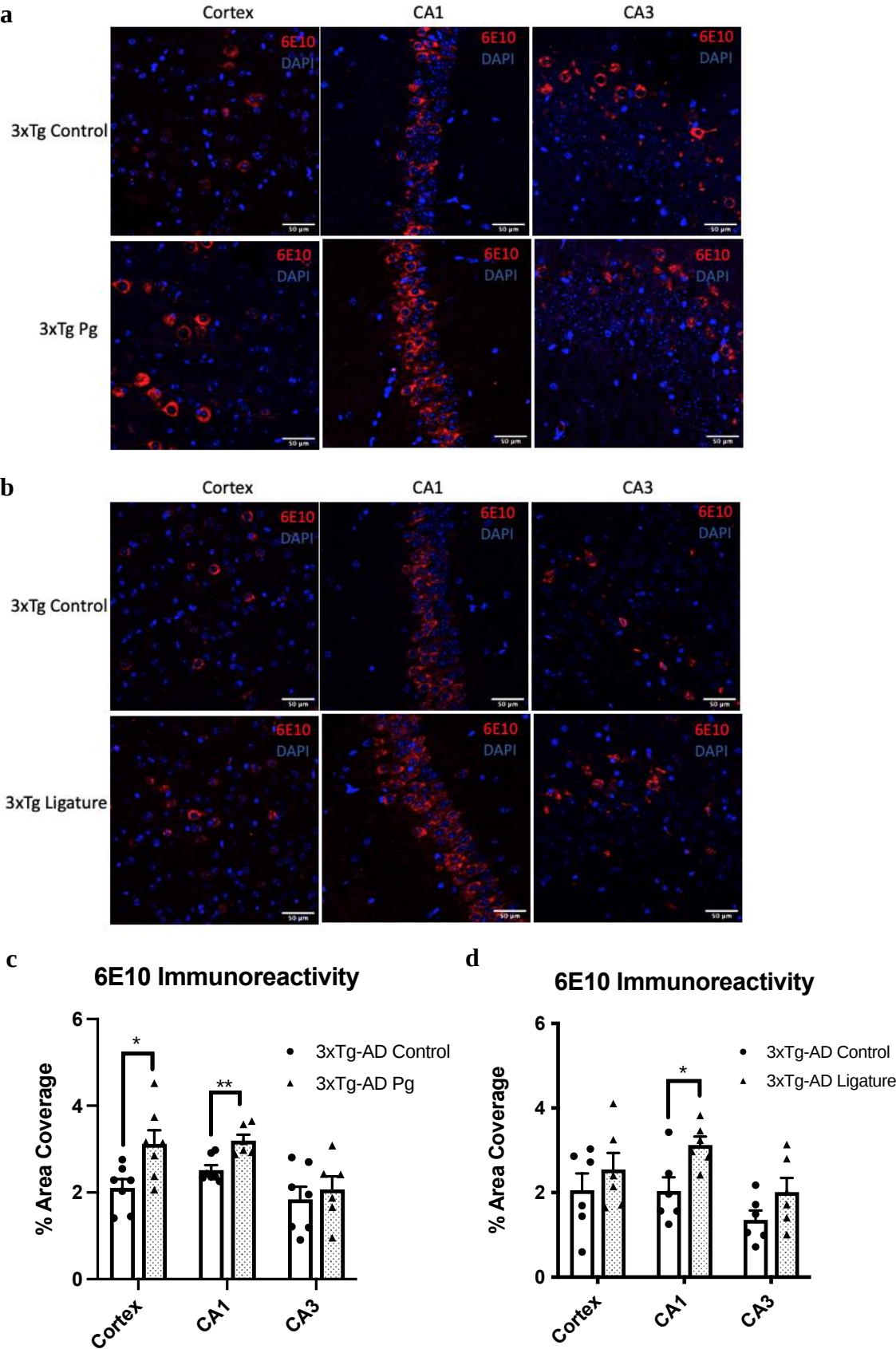


Fig. S14 Periodontitis induced by injection of heat-killed *Pg* as well as ligature placement resulted in increased 6E10 immunoreactivity in the brains of 3×Tg-AD mice. (a-b) Representative images of immunofluorescence staining for 6E10 (red) and DAPI (blue) in the cortex and sub-regions of hippocampus of 3×Tg-AD mice with and without (a) *Pg* injections and (b) ligature placement. **(c-d)** Quantification of 6E10 immunofluorescence intensity in the cortex and sub-regions of the hippocampus of 3×Tg-AD mice with and without (c) *Pg* injections and (d) ligature placement. Data are presented as mean $\pm$ SEM (n = 6-7). Statistical analysis was done using unpaired t test. * p < 0.05, ** p < 0.01

Figure S15

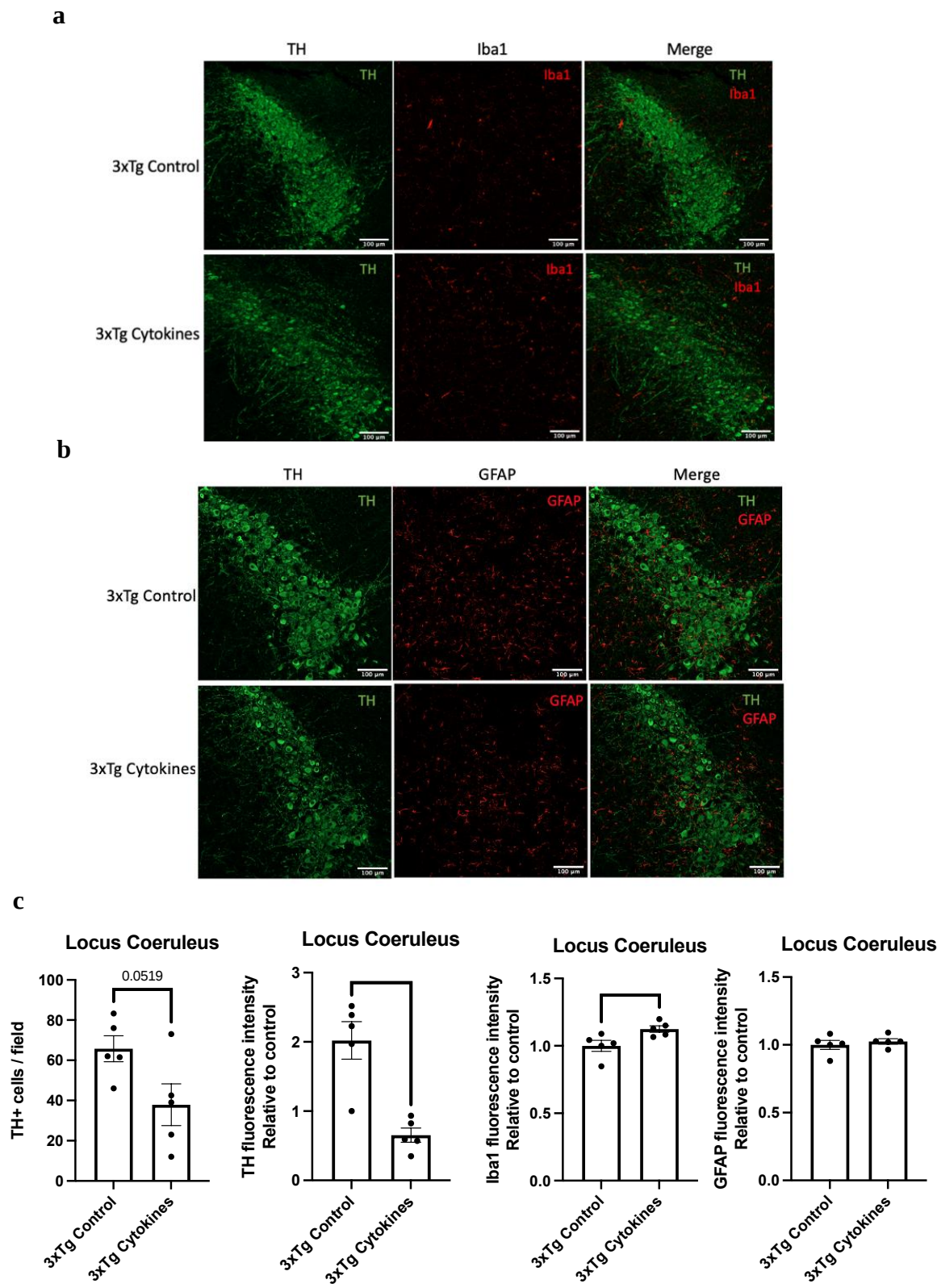


Fig. S15 Injections of mixed cytokines resulted in decreased TH fluorescence intensity and increased Iba-1 intensity in the locus coeruleus of 3×Tg-AD mice. (a) Representative images of immunofluorescence staining for TH (green) and Iba-1 (red) in the locus coeruleus of 3×Tg-AD mice with and without mixed cytokines injection. (b) Representative images of immunofluorescence staining for TH (green) and GFAP (red) in the locus coeruleus of 3×Tg-AD mice with and without mixed cytokines injection. (c) Quantification of TH⁺ cells/field, TH, Iba-1, and GFAP immunofluorescence intensity in the locus coeruleus of 3×Tg-AD mice without and without mixed cytokines injection. Data are presented as mean ± SEM (n = 5). Statistical analysis was done using unpaired t test. * $p < 0.05$, ** $p < 0.01$