Supplementary Materials

Supplementary Figures

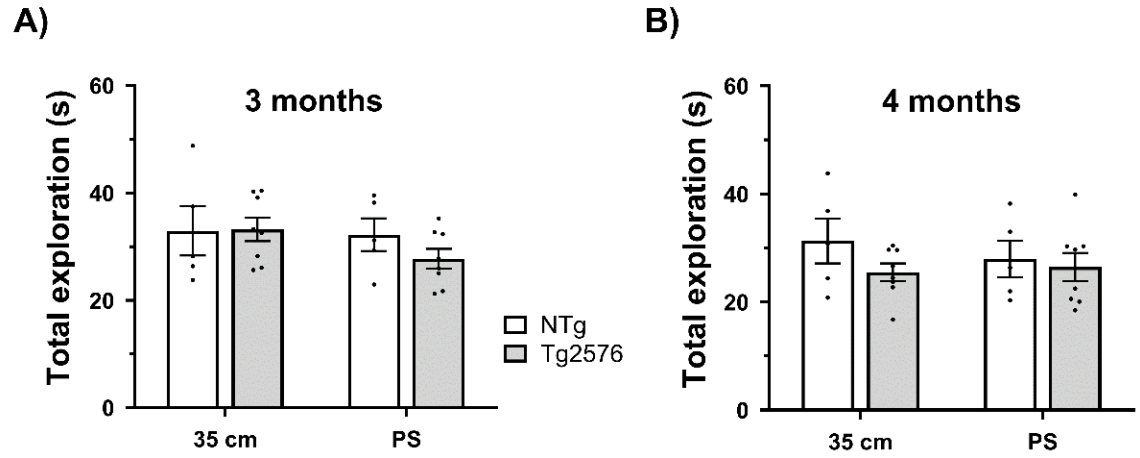

Figure S1. No effect of genotype or distance on total exploration time during acquisition trials regardless of age. Data are expressed as the mean (± SEM) of total exploration time of objects. Data were analyzed by a Student's *t* test. PS: pattern separation.

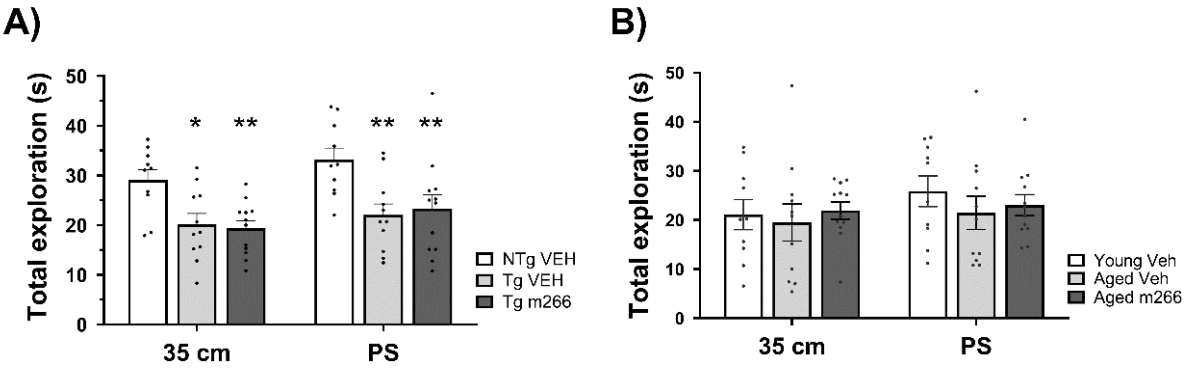

Figure S2. Total object exploration time was not affected by m266 treatment in either mouse models. A) Reduced total exploration time in 5-month-old Tg2576 mice was not rescued by the chronic m266 treatment. **B)** Age and chronic m266 treatment had no effect on total exploration time in B6 mice whatever the acquisition trials. Data are expressed as the mean (± SEM) of total exploration time. Tukey's multiple comparisons test: * $p<0.05$ and ** $p<0.01$ versus NTg vehicle-treated group. PS: pattern separation; Veh: vehicle.

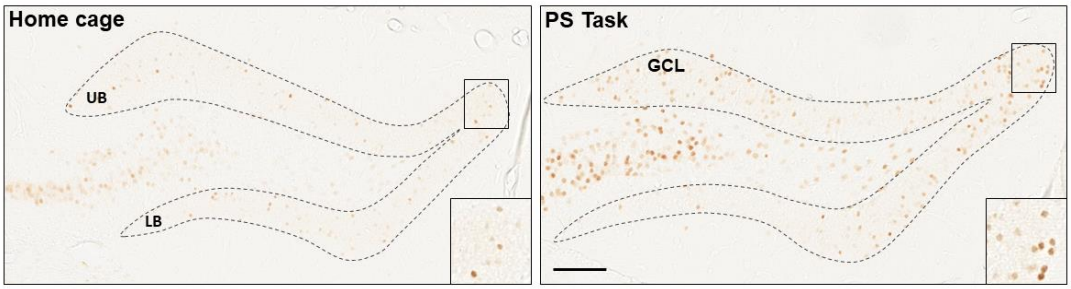

Figure S3. Pattern separation task induces a global activation in the dorsal GCL in vehicle-treated aged B6 mice. Representative micrographs of Egr-1 immunostaining on

dentate gyrus coronal sections from vehicle-treated aged B6 mice in home cage condition (left panel) and ninety minutes after the PS task (right panel) using DAB staining. The GCL is delineated by the black dot lines. The density of Egr-1-positive cells was measured in the lower and upper blades of the GCL. Scale bar: 100 µm. GCL: granule cell layer, LB: Lower blade, PS: pattern separation and UB: upper blade.

Supplementary Tables

Table S1. Density of Egr-1 positive cells in 10^6 µm^3 of dorsal hippocampus GCL for each group of mice (n ≥ 4/group). Cell counts were performed on coronal brain sections from either triple immunostained (BrdU/Dcx/Egr-1) for the Tg experiment or DAB immunostained for the B6 experiment.

	Home cage			Tested		
	NTg vehicle	**Tg2576 vehicle**	**Tg2576 m266**	**NTg vehicle**	**Tg2576 vehicle**	**Tg2576 m266**
Tg2576 experiment (mean ± SEM)	n = 5	n = 4	n = 6	n = 5	n = 5	n = 5
GCL	14.6 ± 4.7	16.2 ± 4.0	11.8 ± 1.0	30.9 ± 4.6	35.4 ± 3.7	23 ± 2.0
Lower blade	14.7 ± 4.7	13.9 ± 3.1	11.0 ± 0.8	22.9 ± 3.7	25.2 ± 2.9	18.4 ± 1.2
Upper blade	17.6 ± 6.0	22.1 ± 6.4	14.9 ± 3.1	43.8 ± 6.5	50.8 ± 5.5	32.1 ± 3.8
	Young vehicle	**Aged vehicle**	**Aged m266**	**Young vehicle**	**Aged vehicle**	**Aged m266**
Aging experiment (mean ± SEM)	n = 4	n = 6	n = 5	n = 4	n = 5	n = 6
GCL	6.6 ± 1.0	6.9 ± 0.6	7.3 ± 0.5	16.6 ± 0.4	20.1 ± 1.6	17.8 ± 1.1
Lower blade	7.4 ± 1.4	7.6 ± 0.7	8.1 ± 0.5	14.7 ± 0.9	17.8 ± 1.4	15.8 ± 1.2
Upper blade	5.8 ± 0.7	6.2 ± 0.6	3.3 ± 0.5	18.4 ± 1.0	22.5 ± 1.2	20.2 ± 1.2

Data are expressed as mean (± SEM) and were analyzed using non-parametric tests.

Table S2. Density of 4-weeks BrdU positive cells in 10^6 µm^3 of dorsal hippocampus GCL from 5-month-old mice. The cell count was carried out on brain coronal sections triple immunostained with anti-BrdU, anti-DCX and anti-Egr-1.

	Home cage			Tested		
	NTg vehicle	**Tg2576 vehicle**	**Tg2576 m266**	**NTg vehicle**	**Tg2576 vehicle**	**Tg2576 m266**
Tg2576 experiment	n = 5	n = 4	n = 6	n = 5	n = 5	n = 6
GCL	3.2 ± 0.5	2.8 ± 0.3	3.2 ± 0.3	3.4 ± 0.6	2.7 ± 0.6	3.1 ± 0.6
Lower blade	2.9 ± 0.5	2.3 ± 0.2	2.7 ± 0.2	2.8 ± 0.7	2.3 ± 0.6	2.6 ± 0.4
Upper blade	3.9 ± 0.5	4.1 ± 0.8	4.0 ± 0.3	4.4 ± 0.8	3.2 ± 0.6	4.1 ± 0.8

Data are expressed as mean (± SEM) and were analyzed with non-parametric tests (see in the results part).

Table S3. Percentage of 4-weeks newborn neurons ($BrdU^+$ DCX^+) in 10^6 µm^3 of dorsal hippocampus GCL from 5-month-old mice. The cell count was carried out on brain coronal sections triple immunostained (BrdU/DCX/Egr-1). Data are percentage of double stained cells ($BrdU^+$ DCX^+) among total $BrdU^+$ cells.

	Home cage			Tested		
	NTg vehicle	Tg2576 vehicle	Tg2576 m266	NTg vehicle	Tg2576 vehicle	Tg2576 m266
Tg2576 experiment	n = 5	n = 4	n = 6	n = 5	n = 5	n = 6
GCL	19.5 ± 2.4	26.2 ± 3.1	23.4 ± 5.2	23.1 ± 3.0	32.5 ± 4.7	17.1 ± 4
Lower blade	18.3 ± 1.9	22.4 ± 3.4	19.7 ± 4.8	18.6 ± 4.1	32.3 ± 7.5	13.1 ± 2.0
Upper blade	20.9 ± 2.7	29.0 ± 4.1	26.5 ± 7.0	27.4 ± 4.2	31.4 ± 2.2	18.7 ± 5.6

Data are expressed as mean (± SEM) and were analyzed with non-parametric tests (see in the results part).

Table S4. Recruitment of 4-weeks newborn neurons during spatial PS task in dorsal hippocampus GCL of 5-month-old mice. Data are percentage of triple stained cells (BrdU+ DCX+ Egr-1+) among double stained cells (total BrdU+ DCX+).

	Home cage			Tested		
	NTg vehicle	Tg2576 vehicle	Tg2576 m266	NTg vehicle	Tg2576 vehicle	Tg2576 m266
Tg2576 experiment	n = 5	n = 4	n = 6	n = 5	n = 5	n = 6
GCL	2.3 ± 0.9	0 ± 0	1.8 ± 0.9	3.2 ± 0.8	0.4 ±0.4	0.8 ± 0.8
Lower blade	5.7 ± 2.8	0 ± 0	2.1 ± 1.4	3.1 ± 2.0	0 ± 0	0 ± 0
Upper blade	2.2 ± 1.5	0 ± 0	2.9 ± 2.1	8.1 ± 1.6	1.4 ± 0.9	1.6 ± 1.6

Data are expressed as mean (± SEM) and were analyzed with non-parametric tests (see in the results part).

Table S5. Analysis of Aβ level by ELISA in the dorsal CA3/DG subregions of 5-week-old Tg2576 mice and in B6 mice.

	Tg2576 vehicle	Tg2576 m266	
Tg2576 experiment	n = 4	n = 5	
Aβ42 (pg/mg tissue)	563.8 ± 40.2	477.4 ± 45.9	
Aβ40 (pg/mg tissue)	2173 ± 240.6	1999 ± 325.7	
Aβ42/ Aβ40 (pg/mg tissue)	0.3 ± 0.02	0.2 ± 0.02	
Aβ42+ Aβ40	2736 ± 271.3	2127 ± 133.0	
	Young vehicle	**Aged vehicle**	**Aged m266**
Aging experiment	n = 5	n = 4	n = 6
Aβ42 (pg/mg tissue)	115.9 ± 15.3	109.0 ± 19.2	129.0 ± 26.8
Aβ40 (pg/mg tissue)	370.4 ± 65.6	271.2 ± 55.6	327.7 ± 58.1
Aβ42/ Aβ40 (pg/mg tissue)	0.3 ± 0.04	0.4 ± 0.02	0.4 ± 0.03
Aβ42+ Aβ40	486.3 ± 76.8	380.2 ± 74.5	456.7 ± 82.65

Data are expressed as mean (± SEM) and were analyzed with non-parametric tests (see in the results part).