

1 **Supplementary Table 1.1:** 3-way ANOVA analysis for figure 1.

Experiment	3-way ANOVA			Significant Tukey's multiple comparisons test	
	Factor	F (DFn, DFd)	P Value	Comparisons	P Value
PD15: Iba1+ area (%) Hippocampus	1: Sex	1: F(1,26)=3.026	1: 0.938	WT F Non-MS vs. WT M MS	0.004
	2: Genotype	2: F(1,26)=3.738	2: 0.064	5xFAD F Non-MS vs. WT M MS	0.033
	3: MS	3: F(1,26)=9.807	3: 0.004		
4: Sex x (genotype)	4: F(1,26)=8.852	4: 0.006	5: 0.147	WT M MS vs. 5xFAD M Non-MS	0.001
5: Sex x (MS)	5: F(1,26)=2.232	6: 0.294	6: 0.294		
6: Genotype x MS	6: F(1,26)=1.144	7: 0.7571	7: 0.7571		
PD15: Iba1+ area (%) Prefrontal Cortex	1: Sex	1: F(1,32)=5.080	1: 0.031	-	
2: Genotype	2: F(1,32)=0.302	2: 0.586			
3: MS	3: F(1,32)=0.233	3: 0.631			
4: Sex x (genotype)	4: F(1,32)=0.009	4: 0.922			
5: Sex x (MS)	5: F(1,32)=1.903	5: 0.177			
6: Genotype x MS	6: F(1,32)=10.41	6: 0.526			
7: Sex x (Genotype) x (MS)	7: F(1,32)=0.287	7: 0.595			
PD15: Microglia morphology Ramified (%) Hippocampus	1: Sex	1: F(1,26)=0.546	1: 0.466	-	
2: Genotype	2: F(1,26)=1.003	2: 0.325			
3: MS	3: F(1,26)=0.002	3: 0.964			
4: Sex x (genotype)	4: F(1,26)=0.024	4: 0.876			
5: Sex x (MS)	5: F(1,26)=0.079	5: 0.780			
6: Genotype x MS	6: F(1,26)=0.540	6: 0.468			
7: Sex x (Genotype) x (MS)	7: F(1,26)=0.118	7: 0.733			
PD15: Microglia morphology With stout processes (%) Hippocampus	1: Sex	1: F(1,26)=0.335	1: 0.567	-	
2: Genotype	2: F(1,26)=0.120	2: 0.730			
3: MS	3: F(1,26)=1.892	3: 0.180			
4: Sex x (genotype)	4: F(1,26)=0.430	4: 0.517			
5: Sex x (MS)	5: F(1,26)=0.361	5: 0.553			
6: Genotype x MS	6: F(1,26)=0.120	6: 0.731			
7: Sex x (Genotype) x (MS)	7: F(1,26)=0.013	7: 0.909			
PD15: Microglia morphology Round/Ameboid (%) Hippocampus	1: Sex	1: F(1,26)=0.640	1: 0.430	-	
2: Genotype	2: F(1,26)=0.691	2: 0.413			
3: MS	3: F(1,26)=0.680	3: 0.416			
4: Sex x (genotype)	4: F(1,26)=0.078	4: 0.780			
5: Sex x (MS)	5: F(1,26)=0.029	5: 0.867			
6: Genotype x MS	6: F(1,26)=0.068	6: 0.795			
7: Sex x (Genotype) x (MS)	7: F(1,26)=0.080	7: 0.779			
PD15: Microglia morphology: Ramified (%) Prefrontal Cortex	1: Sex	1: F(1,32)=0.547	1: 0.464	-	
2: Genotype	2: F(1,32)=1.758	2: 0.194			
3: MS	3: F(1,32)=1.911	3: 0.176			
4: Sex x (genotype)	4: F(1,32)=3.555	4: 0.068			
5: Sex x (MS)	5: F(1,32)=4.332	5: 0.045			
6: Genotype x MS	6: F(1,32)=0.296	6: 0.590			
7: Sex x (Genotype) x (MS)	7: F(1,32)=0.201	7: 0.656			
PD15: Microglia morphology with stout processes (%) Prefrontal Cortex	1: Sex	1: F(1,32)=0.027	1: 0.868	WT F Non-MS vs. WT F MS	0.011
2: Genotype	2: F(1,32)=0.746	2: 0.394			
3: MS	3: F(1,32)=1.642	3: 0.209			
4: Sex x (genotype)	4: F(1,32)=1.225	4: 0.276			
5: Sex x (MS)	5: F(1,32)=1.681	5: 0.204			
6: Genotype x MS	6: F(1,32)=4.561	6: 0.040			
7: Sex x (Genotype) x (MS)	7: F(1,32)=8.837	7: 0.005			
PD15: Microglia morphology:	1: Sex	1: F(1,32)=0.103	1: 0.749	WT F Non-MS vs. WT F MS	0.046
2: Genotype	2: F(1,32)=2.339	2: 0.136			
3: MS	3: F(1,32)=0.010	3: 0.919			

Round/Ameboid (%) Prefrontal Cortex	4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	4: F(1,32)=0.251 5: F(1,32)=5.706 6: F(1,32)=3.918 7: F(1,32)=4.262	4: 0.619 5: 0.023 6: 0.056 7: 0.047		
PD15: CXCL1 Hippocampus	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,32)=1.823 2: F(1,32)=0.222 3: F(1,32)=0.815 4: F(1,32)=5.697 5: F(1,32)=1.116 6: F(1,32)=0.358 7: F(1,32)=0.358	1: 0.186 2: 0.640 3: 0.373 4: 0.023 5: 0.298 6: 0.553 7: 0.553	-	
PD15: TNF-α Hippocampus	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,32)=4.890 2: F(1,32)=2.138 3: F(1,32)=0.007 4: F(1,32)=1.623 5: F(1,32)=2.741 6: F(1,32)=0.036 7: F(1,32)=2.600	1: 0.034 2: 0.153 3: 0.931 4: 0.211 5: 0.107 6: 0.849 7: 0.116	-	

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4 **Supplementary Table 2.1:** 3-way ANOVA analysis for figure 2.

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Experiment	3-way ANOVA			Significant Tukey's multiple comparisons test	
	Factor	F (DFn, DFd)	P Value	Comparisons	P Value
4 months: Open Field Test	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,63)=4.783 2: F(1,63)=1.324 3: F(1,63)=2.393 4: F(1,63)=2.090 5: F(1,63)=1.976 6: F(1,63)=1.770 7: F(1,63)=1.063	1: 0.032 2: 0.254 3: 0.126 4: 0.153 5: 0.164 6: 0.188 7: 0.306	WT F Non-MS vs. WT M MS	0.044
				WT F Non-MS vs. 5Xfad M Non-MS	0.031
4 months: Forced Swim Test	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,58)=1.095 2: F(1,58)=10.97 3: F(1,58)=28.97 4: F(1,58)=2.537 5: F(1,58)=0.010 6: F(1,58)=0.959 7: F(1,58)=2.827	1: 0.299 2: 0.001 3: <0.0001 4: 0.116 5: 0.920 6: 0.331 7: 0.098	WT F MS vs. 5xFAD F Non-MS	0.0002
				WT F MS vs. WT M Non-MS	0.004
				WT F MS vs. 5xFAD M Non-MS	0.003
				5xFAD F vs. WT M MS	0.0002
				WT M Non-MS vs. WT M MS	0.007
				WT M MS vs. 5xFAD M Non-MS	0.004
4 months: Novel Object Recognition Memory Test	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,39)=3.980 2: F(1,39)=8.221 3: F(1,39)=29.44 4: F(1,39)=1.990 5: F(1,39)=0.002 6: F(1,39)=0.044 7: F(1,39)=7.6*10 ⁻⁸	1: 0.053 2: 0.006 3: <0.0001 4: 0.166 5: 0.961 6: 0.834 7: 0.999	WT F Non-MS vs. 5xFAD F MS	0.027
				WT F Non-MS vs. 5xFAD M MS	<0.0001
				5xFAD F Non-MS vs. 5xFAD M MS	0.0006
				WT M Non-MS vs. 5xFAD M MS	0.0004
4 months: HP gene expression Bdnf	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,37)=1.200 2: F(1,37)=0.384 3: F(1,37)=18.10 4: F(1,37)=0.491 5: F(1,37)=4.147 6: F(1,37)=0.197 7: F(1,37)=0.081	1: 0.280 2: 0.539 3: 0.0001 4: 0.487 5: 0.048 6: 0.659 7: 0.776	WT F MS vs. WT M Non-MS	0.033
				WT M Non-MS vs. 5xFAD M MS	0.004
4 months: HP gene expression Arc	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,40)=0.008 2: F(1,40)=1.063 3: F(1,40)=0.483 4: F(1,40)=0.186 5: F(1,40)=1.753 6: F(1,40)=0.017 7: F(1,40)=10.32	1: 0.927 2: 0.308 3: 0.490 4: 0.668 5: 0.193 6: 0.894 7: 0.002	-	

7 **Supplementary Table 3.1:** 3-way ANOVA analysis for figure 3.

Experiment	3-way ANOVA			Significant Tukey's multiple comparisons test	
	Factor	F (DFn, DFd)	P Value	Comparisons	P Value
4 months: Iba1+ area (%) Prefrontal Cortex	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,43)=3.143 2: F(1,43)=81.78 3: F(1,43)=4.368 4: F(1,43)=5.522 5: F(1,43)=3.873 6: F(1,43)=0.244 7: F(1,43)=6.031	1: 0.083 2: <0.0001 3: 0.042 4: 0.023 5: 0.055 6: 0.623 7: 0.018	WT F Non-MS vs. 5xFAD F Non-MS	0.0067
				WT F Non-MS vs. 5xFAD F MS	<0.0001
				WT F Non-MS vs. 5xFAD M Non-MS	0.003
				WT F Non-MS vs. 5xFAD M MS	0.035
				WT F MS vs. 5xFAD Non-MS F	0.012
				WT F MS vs. 5xFAD F MS	<0.0001
				WT F MS vs. 5xFAD M Non-MS	0.005
				5xFAD F Non-MS vs. 5xFAD F MS	0.027
				5xFAD F Non-MS vs. WT M Non-MS	0.002
				5xFAD F MS vs. WT M Non-MS	<0.0001
				5xFAD F MS vs. WT M MS	<0.0001
				5xFAD F MS vs. 5xFAD M Non-MS	0.029
				5xFAD F MS vs. 5xFAD M MS	0.002
				WT M Non-MS vs. 5xFAD M Non-MS	0.001
				WT M Non-MS vs. 5xFAD M MS	0.017
				WT M MS vs. 5xFAD M Non-MS	0.034

4 months: CD68+ area related to Iba1+ area (%) Prefrontal Cortex	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,31)=4.591 2: F(1,31)=31.58 3: F(1,31)=0.230 4: F(1,31)=0.879 5: F(1,31)=1.467 6: F(1,31)=4.372 7: F(1,31)=2.890	1: 0.040 2: <0.0001 3: 0.634 4: 0.355 5: 0.235 6: 0.044 7: 0.099	WT F Non-MS vs. 5xFAD F Non-MS	0.025
				WT F Non-MS vs. 5xFAD F MS	0.004
				WT F Non-MS vs. 5xFAD M Non-MS	0.031
				5xFAD F Non-MS vs. WT M Non-MS	0.002
				5xFAD F MS vs. WT M Non-MS	0.0004
				5xFAD F MS vs. WT M MS	0.044
				WT M Non-MS vs. 5xFAD M Non-MS	0.003

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10 **Supplementary Table 4.1:** 3-way ANOVA analysis for figure 4.

Experiment	3-way ANOVA			Significant Tukey's multiple comparisons test	
	Factor	F (DFn, DFd)	P Value	Comparisons	P Value
4 months: Inflammatory Monocytes	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,60)=9.208 2: F(1,60)=0.376 3: F(1,60)=22.07 4: F(1,60)=3.128 5: F(1,60)=1.091 6: F(1,60)=0.069 7: F(1,60)=1.481	1: 0.003 2: 0.541 3: <0.0001 4: 0.082 5: 0.300 6: 0.792 7: 0.228	WT F Non-MS vs. 5xFAD M MS	0.001
				5xFAD F Non-MS vs. WT M MS	0.043
				5xFAD F Non-MS vs. 5xFAD M MS	0.001
				5xFAD F MS vs. 5xFAD M MS	0.041
				WT M Non-MS vs. 5xFAD M MS	0.016
4 months: Cytotoxic T Cells	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,60)=9.820 2: F(1,60)=3.152 3: F(1,60)=20.54 4: F(1,60)=0.189 5: F(1,60)=0.956 6: F(1,60)=2.551 7: F(1,60)=1.176	1: 0.002 2: 0.080 3: <0.0001 4: 0.665 5: 0.332 6: 0.115 7: 0.282	WT F Non-MS vs. 5xFAD M MS	0.046
				WT F MS vs. 5xFAD F Non-MS	0.002
				5xFAD F Non-MS vs. 5xFAD F MS	0.028
				5xFAD F Non-MS vs. WT M Non-MS	0.005
				5xFAD F Non-MS vs. WT M MS	0.0007
				5xFAD F Non-MS vs. 5xFAD M MS	0.001
4 months: Dendritic Cells	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,60)=4.610 2: F(1,60)=8.868 3: F(1,60)=4.649 4: F(1,60)=0.122 5: F(1,60)=0.022 6: F(1,60)=0.015 7: F(1,60)=2.370	1: 0.035 2: 0.004 3: 0.035 4: 0.728 5: 0.880 6: 0.902 7: 0.128	-	
4 months: Eosinophils	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,60)=5.729 2: F(1,60)=0.771 3: F(1,60)=7.144 4: F(1,60)=1.684 5: F(1,60)=0.672 6: F(1,60)=1.134 7: F(1,60)=0.020	1: 0.019 2: 0.383 3: 0.009 4: 0.199 5: 0.415 6: 0.291 7: 0.887	-	
4 months: Neutrophils	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS	1: F(1,60)=14.56 2: F(1,60)=1.769 3: F(1,60)=3.980 4: F(1,60)=0.005 5: F(1,60)=0.021 6: F(1,60)=1.730	1: 0.0003 2: 0.188 3: 0.050 4: 0.942 5: 0.883 6: 0.193	WT F Non-MS vs. 5xFAD M MS	0.005
				5xFAD F Non-MS vs. 5xFAD M MS	0.042

	7: Sex x (Genotype) x (MS)	7: F(1,60)=2.349	7: 0.130		
4 months: Activated T helper	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,60)=2.886 2: F(1,60)=14.17 3: F(1,60)=5.226 4: F(1,60)=8.1*10 ⁻⁶ 5: F(1,60)=0.649 6: F(1,60)=2.519 7: F(1,60)=1.053	1: 0.094 2: 0.0004 3: 0.025 4: 0.997 5: 0.423 6: 0.117 7: 0.309	WT F MS vs. 5xFAD M Non-MS	0.031
				WT M MS vs. 5xFAD M Non-MS	0.026
4 months: Activated T cytotoxic	1: Sex 2: Genotype 3: MS 4: Sex x (genotype) 5: Sex x (MS) 6: Genotype x MS 7: Sex x (Genotype) x (MS)	1: F(1,60)=0.025 2: F(1,60)=2.263 3: F(1,60)=1.268 4: F(1,60)=0.257 5: F(1,60)=0.109 6: F(1,60)=4.381 7: F(1,60)=3.808	1: 0.873 2: 0.137 3: 0.264 4: 0.613 5: 0.741 6: 0.040 7: 0.055	-	

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13 **Supplementary Table 5.1:** 3-way ANOVA analysis for figure Supplementary 1.
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Experiment	3-way ANOVA			Significant Tukey's multiple comparisons test	
	Factor	F (DFn, DFd)	P Value	Comparisons	P Value
4 months: Iba1 Dentate Gyrus	1: Sex	1: F(1,46)=3.326	1: 0.074	WT F Non-MS vs. 5xFAD F MS	0.049
	2: Genotype	2: F(1,46)=20.29	2: <0.0001	WT F MS vs. 5xFAD F MS	0.040
	3: MS	3: F(1,46)=0.021	3: 0.883	5xFAD F MS vs. WT M Non-MS	0.009
4 months: Iba1 CA1	4: Sex x (genotype)	4: F(1,46)=1.075	4: 0.305	WT F Non-MS vs. 5xFAD F MS	0.032
	5: Sex x (MS)	5: F(1,46)=0.471	5: 0.495	WT F MS vs. 5xFAD F MS	0.007
	6: Genotype x MS	6: F(1,46)=0.198	6: 0.658	5xFAD F MS vs. WT M Non-MS	0.002
	7: Sex x (Genotype) x (MS)	7: F(1,46)=1.211	7: 0.276	5xFAD F MS vs. WT M MS	0.027
	1: Sex	1: F(1,46)=3.621	1: 0.063	-	-
	2: Genotype	2: F(1,46)=21.84	2: <0.0001	-	-
	3: MS	3: F(1,46)=0.394	3: 0.533	-	-
4 months: Iba1 CA3	4: Sex x (genotype)	4: F(1,46)=1.042	4: 0.312	-	-
	5: Sex x (MS)	5: F(1,46)=0.147	5: 0.702	-	-
	6: Genotype x MS	6: F(1,46)=0.232	6: 0.632	-	-
	7: Sex x (Genotype) x (MS)	7: F(1,46)=1.502	7: 0.226	-	-
	1: Sex	1: F(1,45)=1.348	1: 0.251	-	-
	2: Genotype	2: F(1,45)=7.708	2: 0.008	-	-
	3: MS	3: F(1,45)=0.406	3: 0.526	-	-
4 months: Iba1 Amygdala	4: Sex x (genotype)	4: F(1,45)=0.887	4: 0.351	-	-
	5: Sex x (MS)	5: F(1,45)=0.001	5: 0.971	-	-
	6: Genotype x MS	6: F(1,45)=0.010	6: 0.979	-	-
	7: Sex x (Genotype) x (MS)	7: F(1,45)=1.024	7: 0.317	-	-
	1: Sex	1: F(1,45)=0.124	1: 0.725	WT F MS vs. 5xFAD F MS	0.019
	2: Genotype	2: F(1,45)=20.74	2: <0.0001	WT F MS vs. 5xFAD M Non-MS	0.047
	3: MS	3: F(1,45)=0.046	3: 0.829	5xFAD F MS vs. WT M Non-MS	0.041