Supplemental Figures

Supplemental Figure 1. Additional biochemical and behavioral data for Tg19959 cohort. (A) Levels of p-AMPKα1 or p-AMPKα2 were unaltered in Tg mice compared to WT (n=4, non-congruous with 1 technical replicate). **(B-C)** Levels of AMPKβ and AMPKγ were not altered across different genotype groups (n=4, non-congruous). **(D)** Genetic reduction of AMPKα1 (n = 5, WT vs α1/cre $^*p=0.0108$, α1/cre vs α2/cre $^*p=0.0103$, one-way ANOVA with Tukey's *post-hoc* test, F = 5.85) and AMPKα2 (n = 5, $^*p=0.0228$, $^{***}p<0.0001$ one-way ANOVA with Tukey's *post-hoc* test, F = 8.172). **(E)** Representative H&E stain of hippocampal structures of WT, α1/cre, and α2/cre (n=3). **(F)** OF average velocity (cm/s). **(G)** OF total distance travelled (cm) (WT n = 25, Tg n = 21, α1/cre n= 17, α1/Tg n = 14, α2/cre n = 19, α2/Tg n = 13). **(H-J)** Percentage of time spent in non-target quadrants during the MWM probe trial (WT n = 19, Tg n = 17, α1/cre n = 13, α1/Tg n = 17, α2/cre n =19, α2/Tg n = 13, WT vs α2/Tg $^*p=0.0218$, WT vs Tg $^{**}p=0.0064$, one-way ANOVA with Tukey's *post-hoc* test, F = 3.614). QR: right quadrant; QO: opposite quadrant; QL: left quadrant. **(K)** Escape latency (s) for the visible platform assay (4 trials/day, 2 days). Box and whisker plots represent the interquartile range, with the line across the box indicating the median. Whiskers show the highest and lowest values detected.

Supplemental Figure 2. Amyloid Pathway processing is not affected by AMPKα isoform reduction. (A) Hippocampal expression of APP was unaffected in Tg by either AMPKα1 or AMPKα2 reduction (n = 5 with up to 2 technical replicates). **(B)** β-Secretase expression was increased in Tg, α1/Tg, and α2/Tg as compared to WT controls (WT vs Tg $^*p=0.0364$, WT vs α1/Tg $^{***}p=0.0004$, WT vs α2/Tg $^{***}p=0.0006$, one-way ANOVA with Tukey's *post-hoc* test, F = 8.202). **(C)** γ-Secretase component PS2 expression was increased in Tg, α1/Tg, and α2/Tg as compared to WT controls (WT vs Tg $^{**}p=0.0063$, WT vs α2/Tg $^{**}p=0.0064$, WT vs α1/Tg $^{****}p<0.0001$, one-way ANOVA with Tukey's *post-hoc* test, F = 9.922). Note: Same loading controls as B. **(D)** Amyloid β expression was unaffected. WT n = 10, Tg n = 9, α1/Tg n = 6, α2/Tg n = 7 with 3 technical replicates. (E) Total Tau levels were not significantly altered (n = 4 with 2 technical replicates). Box and whisker plots represent the interquartile range, with the line across the box indicating the median. Whiskers show the highest and lowest values detected.

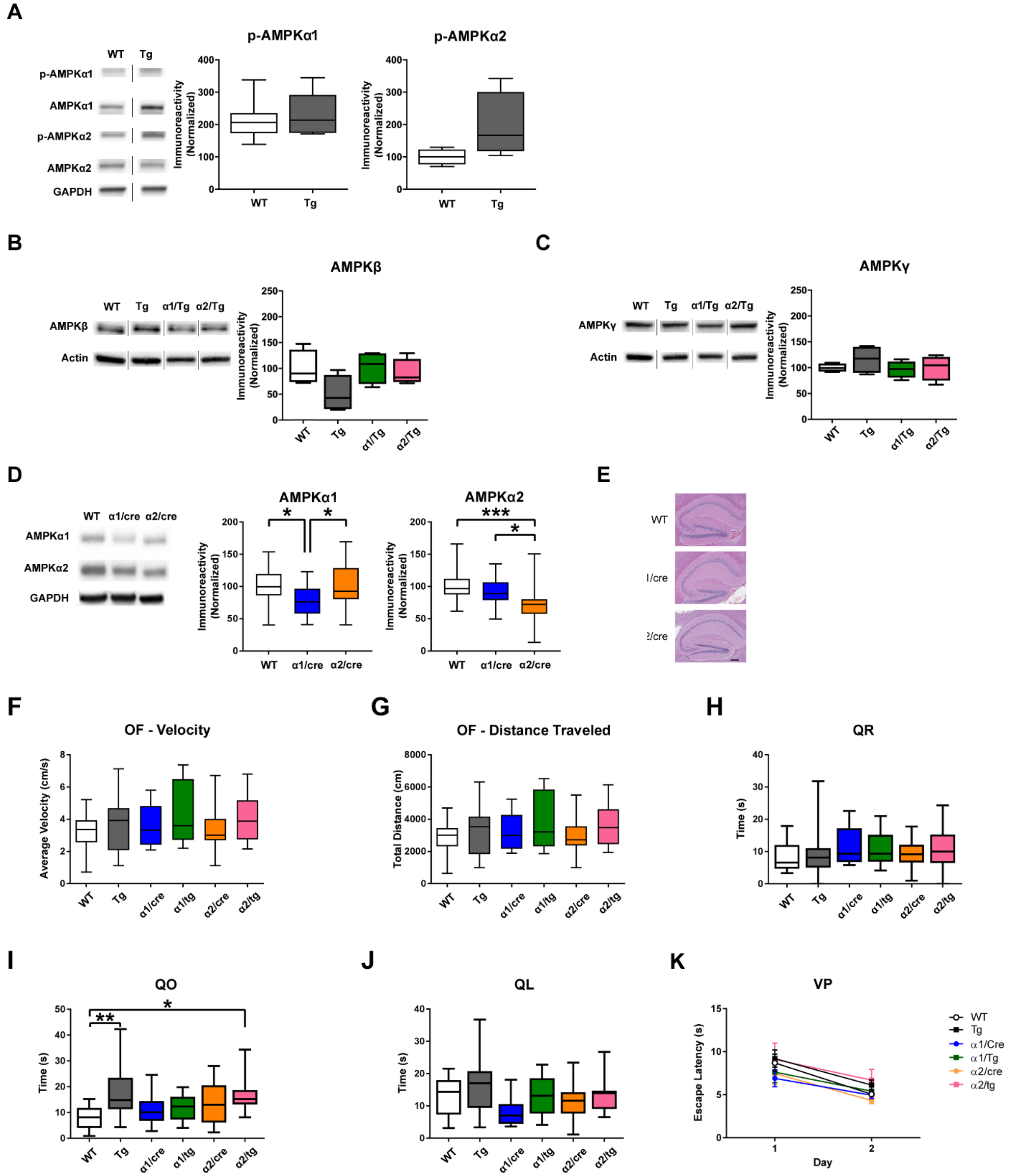
Supplemental Figure 3. Golgi-Cox analysis of immature spine types in area CA1. (A) WT and α1/Tg mice have significantly fewer immature spines than Tg and α2/Tg mice (α1/Tg vs α2/Tg *p=0.0165, Tg vs α1/Tg **p=0.0052, ****p<0.0001, one-way ANOVA with Tukey's *post-hoc* test F = 48.69). **(B)** α1/Tg mice have significantly fewer filopodia than WT mice (****p<0.0001, F = 6.208). **(C)** Tg mice have significantly more thin spines than α1/Tg mice (Tg vs α1/Tg *p=0.0105,one-way ANOVA with Tukey's *post-hoc* test, F = 4.54). WT n =4 mice, Tg, α1/Tg, and α2/Tg n = 3 mice, 200 μm spine length analyzed from 5 ROIs per slice, 3-7 slices per mouse. Box and whisker plots represent the interquartile range, with the line across the box indicating the median. Whiskers show the highest and lowest values detected.

Supplemental Figure 4. Examination of molecular signaling cascades associated with AMPK. (A-B) Phosphorylation of TSC2 and mTOR were unaffected by AMPKα isoform reduction (n = 4, non-congruous). **(C-E)** Hippocampal levels of the A, B, and C subunits of PP2A were unaffected in the 4 genotypes (n = 6). **(F)** Levels of K_{Ca}α1 were significantly reduced in Tg mice. Catalase levels were not changed in Tg mice. (n = 4, *p=0.0253, unpaired Student's t-test). Box and whisker plots represent the interquartile range, with the line across the box indicating the median. Whiskers show the highest and lowest values detected.

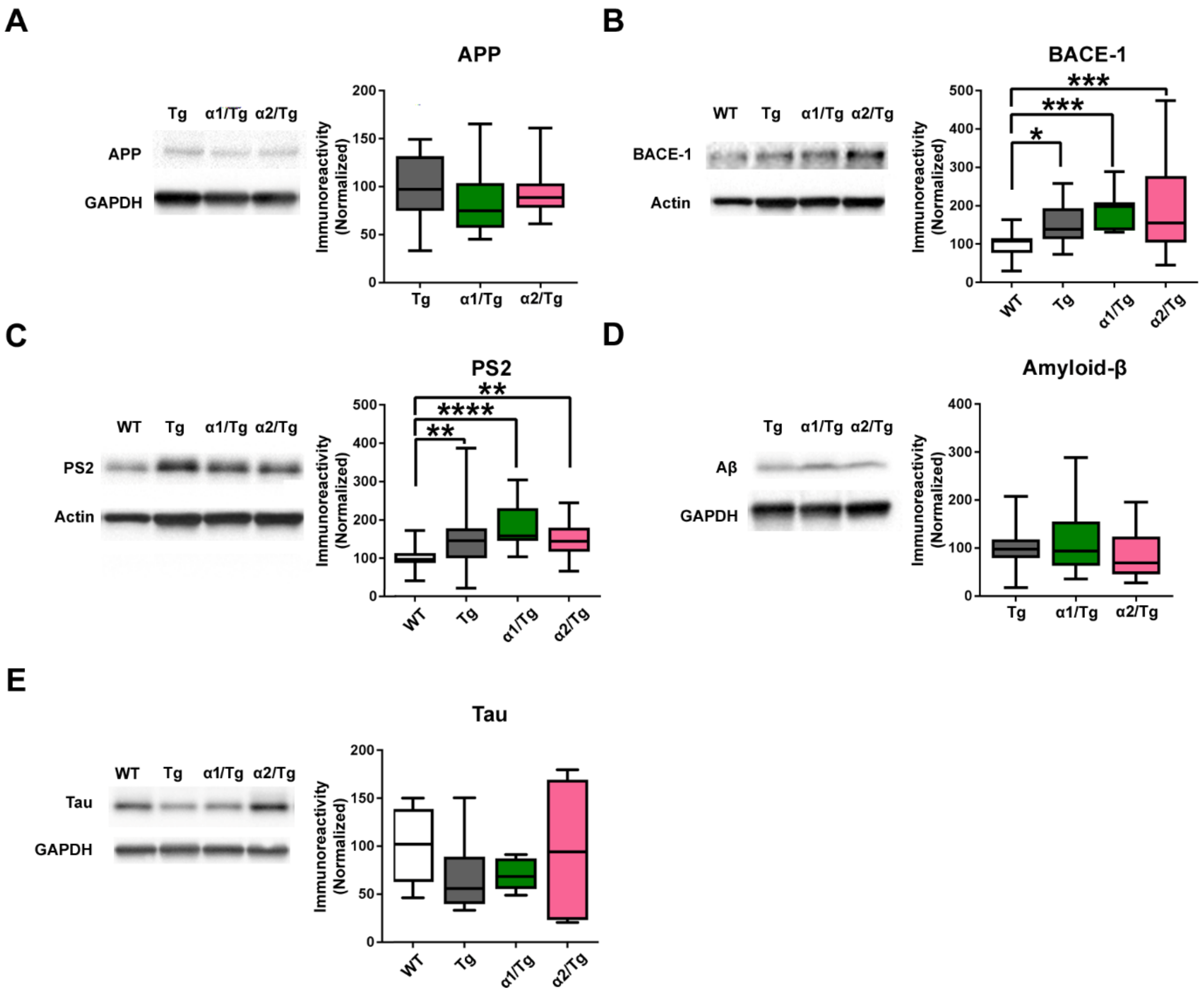
Supplemental Figure 5. Extended data for experiments with APP/PS1 cohort. (A-B) AMPKβ and γ levels were unchanged in APP/PS1 mice or mice with selective AMPKα reduction (n = 4, non-congruous). **(C)** Average velocity (cm/s) in the open field (OF) assay was significantly higher in APP and α2/APP mice (WT n = 28, APP n = 20, α1/APP n = 13, α2/APP n = 20) (****p<0.0001, one-way ANOVA with Tukey's *post-hoc* test F = 8.428). **(D)** Total distance travelled was also significantly higher in APP and α2/APP mice (****$p<0.0001$, one-way ANOVA with Tukey's *post-hoc* test F = 8.319). **(E-G)** Average time spent in the other quadrants during the MWM probe trial (WT n = 18, APP n = 18, α1/APP n = 9, α2/APP n = 15). QR: right quadrant; QO: opposite quadrant; QL: left quadrant. **(H)** Visible platform (VP) escape latency (4 trials per day, 2 days) was unaffected. Box and whisker plots represent the interquartile range, with the line across the box indicating the median. Whiskers show the highest and lowest values detected.

Supplemental Figure 6. Extended biochemical data in APP/PS1 Cohort. (A-C) ELISA quantification of prefrontal cortex Aβ1-40 and Aβ1-42 levels were unaffected by AMPKα isoform reduction (n = 8). **(D)** Phosphorylation of Tau (S396 and S262) in hippocampus was unaltered in all four genotypes (n = 4). **(E)** Levels of total Tau were unchanged in all four genotypes (n = 4 with 2 technical replicates, non-congruous). Box and whisker plots represent the interquartile range, with the line across the box indicating the median. Whiskers show the highest and lowest values detected.

Supplemental Figure 1



Supplemental Figure 2



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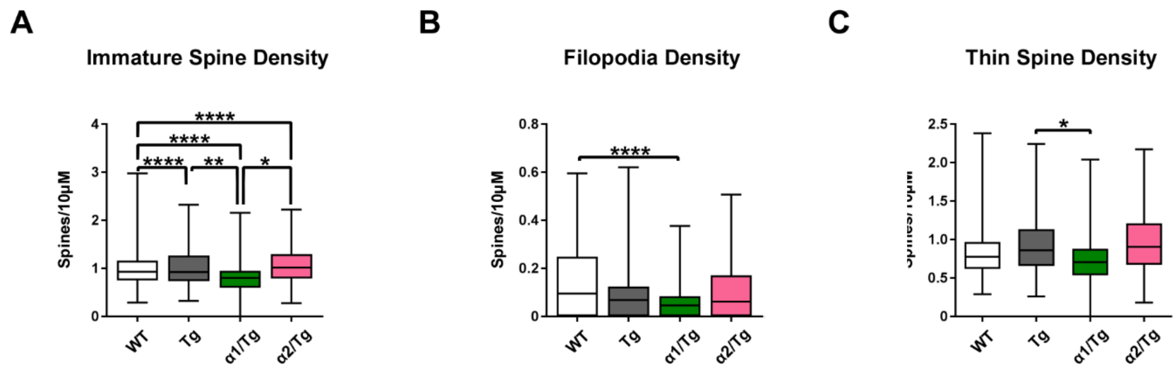

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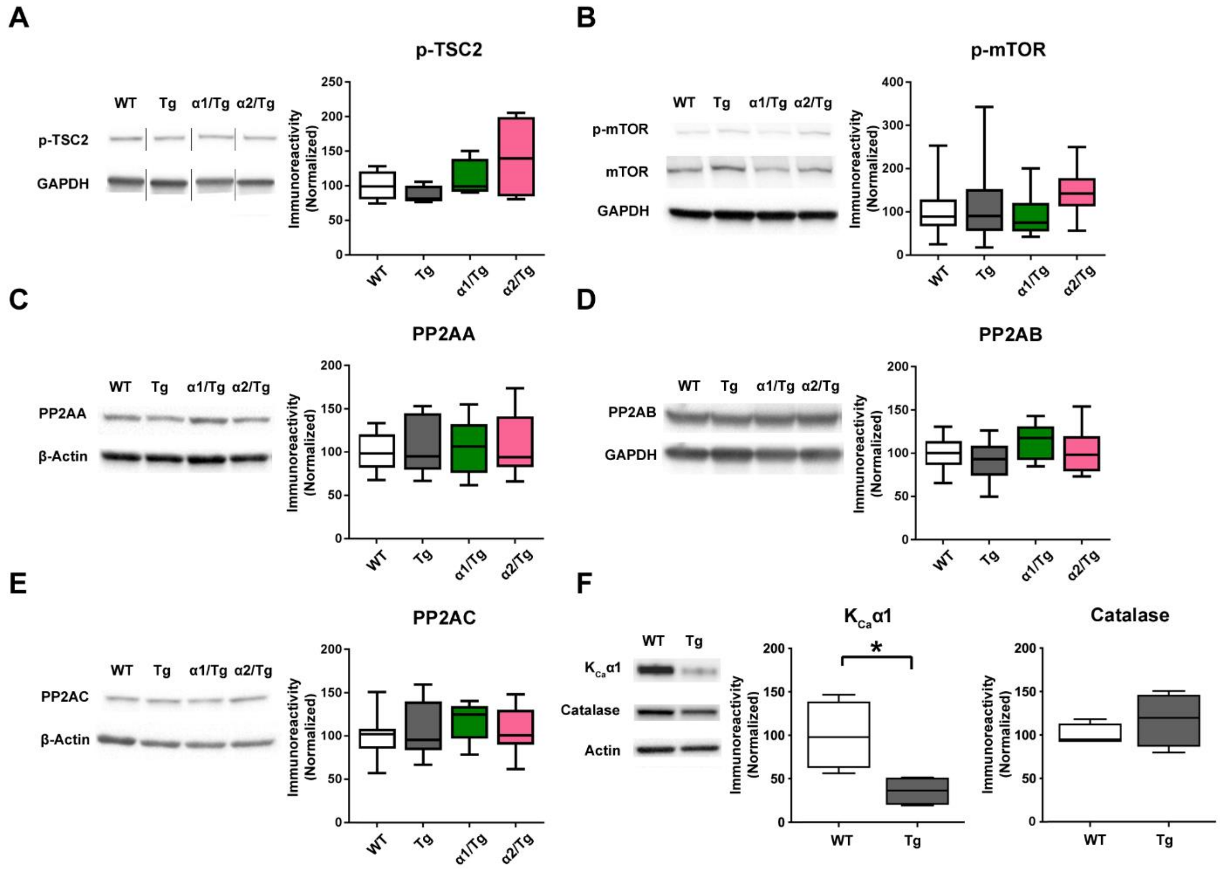
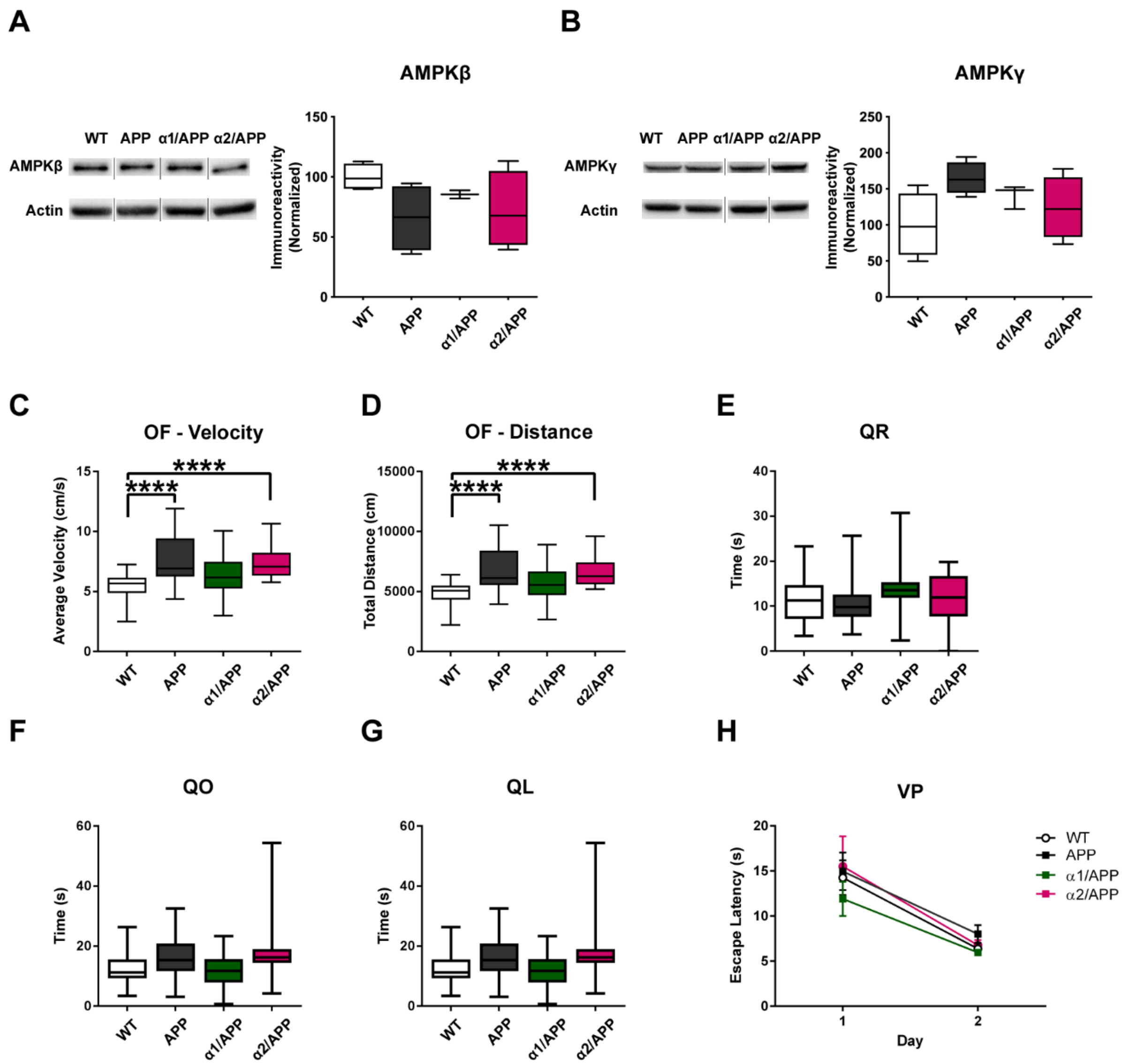


Supplemental Figure 5



Supplemental Figure 6