

SUPPLEMENTARY INFORMATION

Blockade of brain alkaline phosphatase efficiently reduces amyloid- β plaque burden and associated cognitive impairment.

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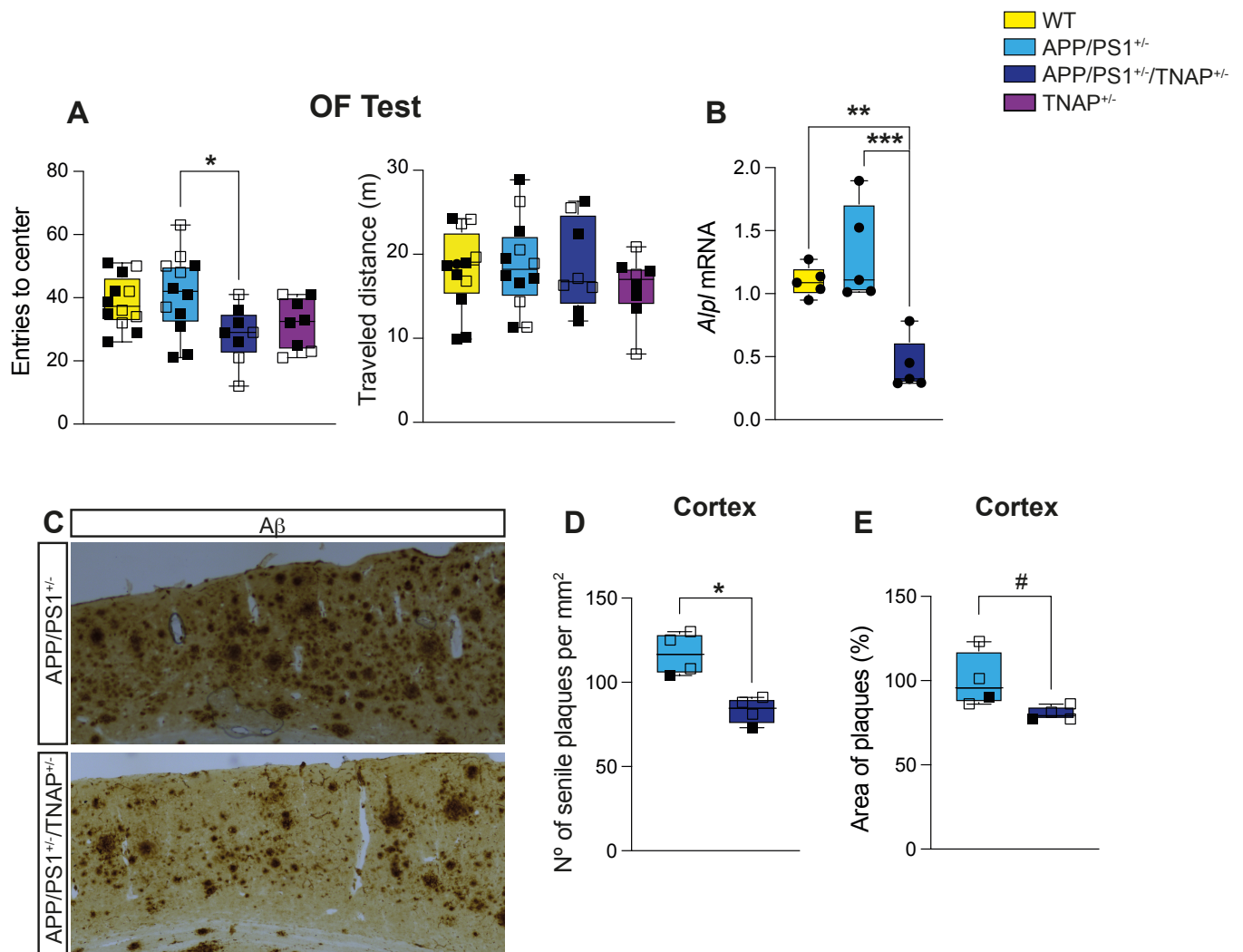
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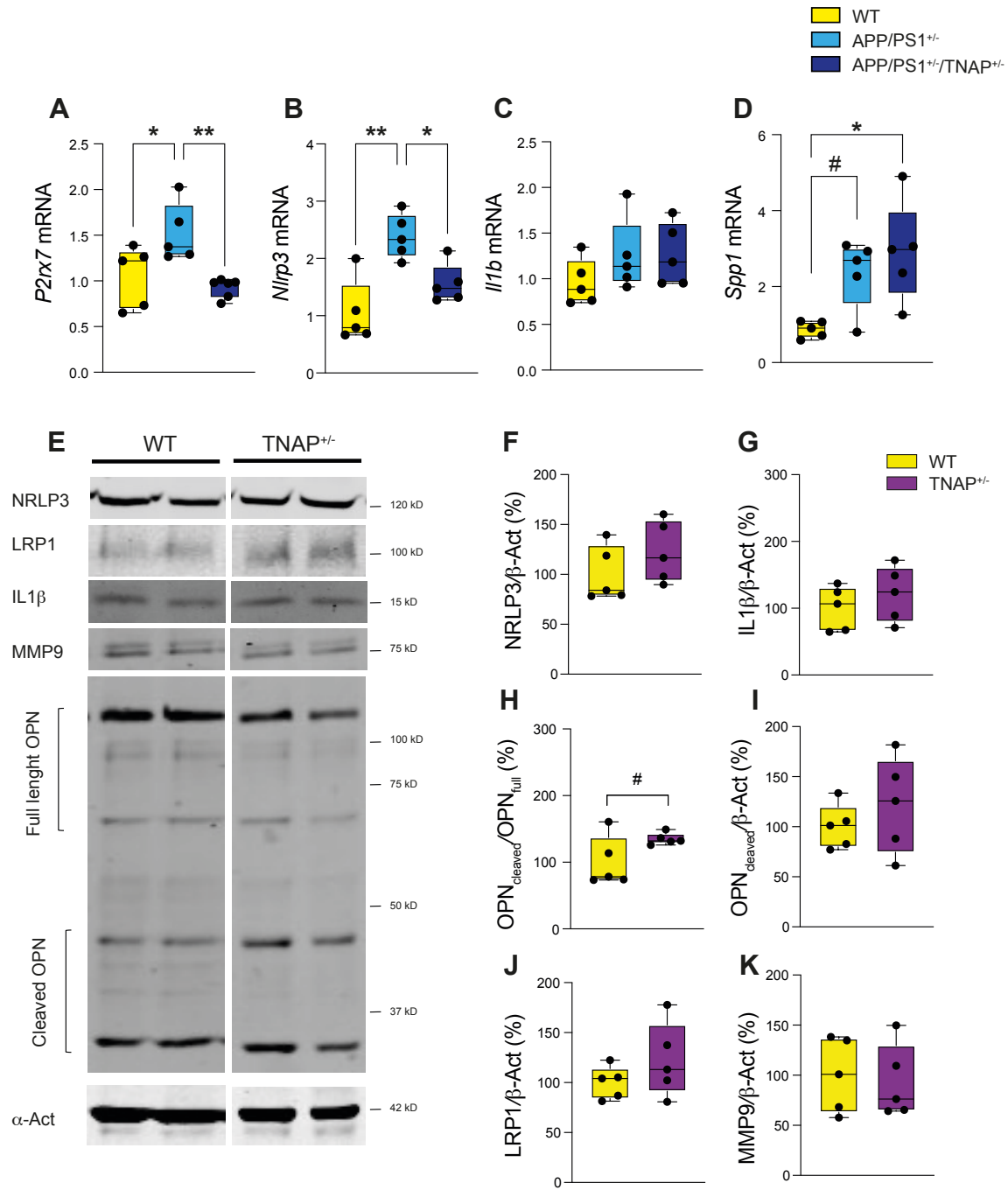
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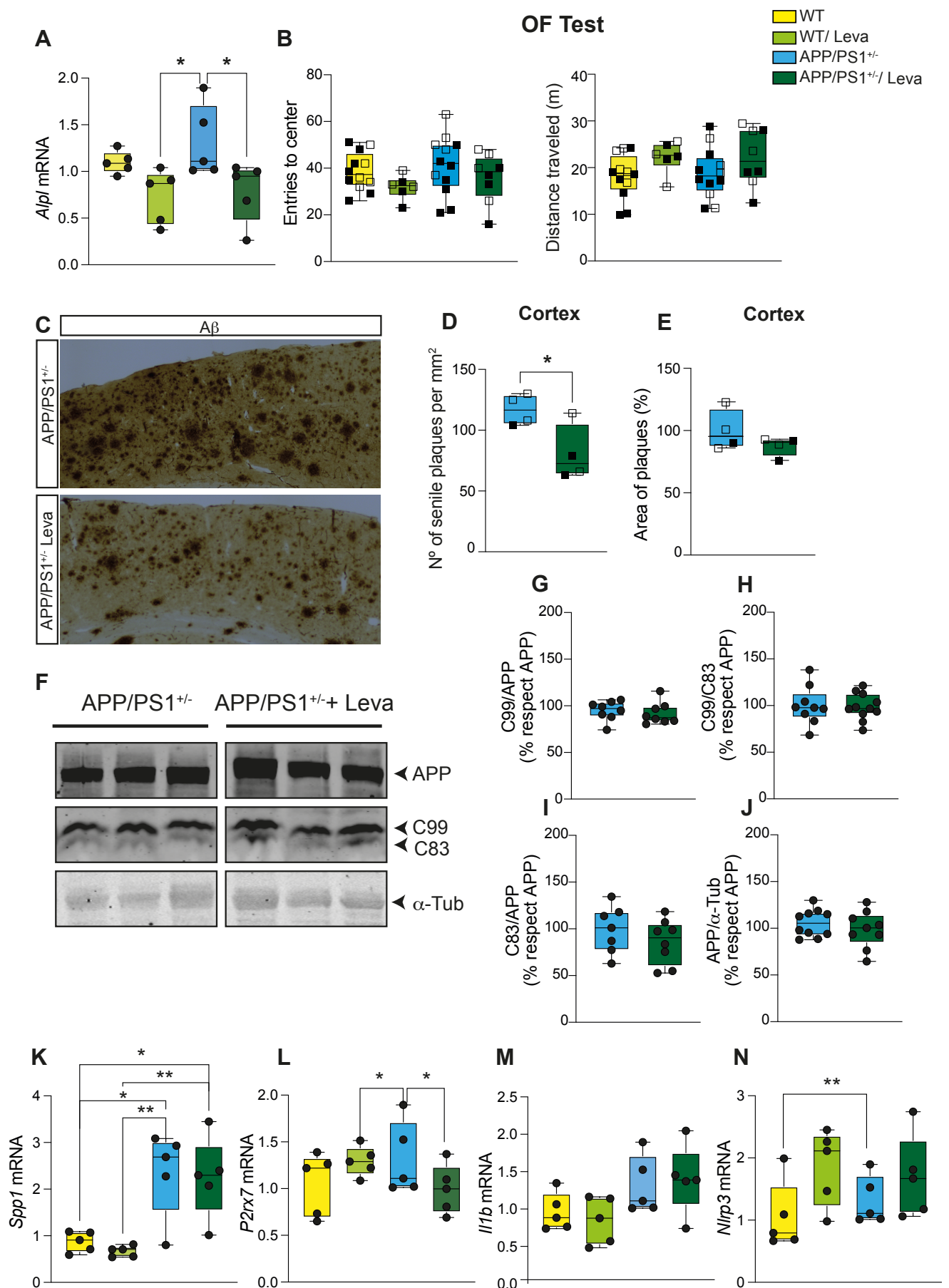


Supplementary Figure 1. Decreased TNAP activity in APP/PS1^{+/-} mice reduces entries to the center in the open field and diminishes the burden of amyloid-β plaques in the cerebral cortex. **A.** Open Field (OF) behavioral assay was performed by WT (n = 12), APP/PS1^{+/-} (n = 12), APP/PS1^{+/-}/TNAP^{+/-} (n = 8) and TNAP^{+/-} (n = 8) groups. Total number of center entries (left graph) and distance travelled (right graph) during the OF test. **B.** qRT-PCR analysis of *Alpl* mRNA from hippocampus of WT (n = 5), APP/PS1^{+/-} (n = 5) and APP/PS1^{+/-}/TNAP^{+/-} (n = 5) mice. * $P \leq 0.05$, ** $P \leq 0.01$ or *** $P \leq 0.001$; using a one-way ANOVA followed by Tukey's post hoc test. Data in box plots represent the distribution of values per group (median, IQR, maximum, and minimum values). **C.** Representative amyloid-β (Aβ) immunohistochemistry in cerebral cortex from APP/PS1^{+/-} (n = 4) and APP/PS1^{+/-}/TNAP^{+/-} (n = 4) mice. **D, E.** Graphs represent the distribution of values per group (median, IQR, maximum, and minimum values) of the number (**D**) and the percentage of area (**E**) of cortical senile plaques. # $P \leq 0.08$ or * $P \leq 0.05$ using T-test.



Supplementary Figure 2. TNAP haplodeficiency prevents the increased mRNA expression of *P2rx7* and *Nlrp3* and increases the mRNA expression of *Spp1* in APP/PS1^{+/-} mice, in addition to favoring the cleaved of OPN in WT mice. A-D. qRT-PCR analysis of *Nlrp3* (A), *P2rx7* (B), *Il1b* (C) and *Spp1* (D) mRNA from hippocampus of WT (n = 5), APP/PS1^{+/-} (n = 5) and APP/PS1^{+/-}/TNAP^{+/-} (n = 5 or 6) mice. Data in box plots represent the distribution of values per group (median, IQR, maximum, and minimum values). # $P \leq 0.08$. * $P \leq 0.05$ or ** $P \leq 0.01$; using a one-way ANOVA followed by Tukey's post hoc test. **E.** Representative immunoblots of NRLP3, LRP1, IL-1β, MMP9 and cleaved and full-length OPN in homogenates from the hippocampus of WT (n=5)

and TNAP+/- (n=5) mice. **F to K** Quantification of the levels of NRLP3 (F) ; IL-1 β (G); the ratio between cleaved OPN and full lenght OPN (H); Total OPN (I); LRP1 (J) and MMP9 (K) given as percentage relative to WT mice. Graphs show the distribution of values per group (median, IQR, maximum and minimum values). Levels of beta-Actine were used as loading control for normalization purposes. #P $\leq$ 0,008 marginal significance, using an unpaired t-test.



Supplementary Figure 3. TNAP pharmacological inhibition in APP/PS1^{+/-} mice does not alter the open field test or amyloidogenic processing of APP but diminished the number of cortical senile plaques and prevents increased mRNA expression of *P2rx7* and *Nrlp3*. **A.** qRT-PCR analysis of *Alpl* mRNA from hippocampus of WT (n = 5), WT treated with levamisole (WT/Leva, n = 5), APP/PS1^{+/-} (n = 5) and APP/PS1^{+/-} treated with levamisole (APP/PS1^{+/-}/Leva, n = 5) mice. **B.** Open Field (OF) behavioral assay was performed by WT (n = 12), WT/Leva (n = 6), APP/PS1^{+/-} (n = 12), APP/PS1^{+/-}/Leva (n = 8) groups. Total number of center entries (left graph) and distance traveled (right graph) during the OF test. **C.** Representative amyloid- β (A β) immunohistochemistry in cerebral cortex from APP/PS1^{+/-} (n = 4) and APP/PS1^{+/-}/Leva (n = 4) mice.. **D, E.** Graphs represent the distribution of values per group (median, IQR, maximum, and minimum values) of the number (**D**) and the percentage of area (**E**) of cortical senile plaques. * $P \leq 0.05$ using T-test. **F.** Representatives immunoblot of APP and fragments C99 and C83 in homogenates from hippocampus of APP/PS1^{+/-} and APP/PS1^{+/-}/Leva mice. **G-J.** Quantification of C99/APP (**G**), C99/C83 (**H**) C83/APP (**I**), and APP/ α -Tub (**J**) protein levels in the hippocampus of APP/PS1^{+/-} (n $\geq$ 6) and APP/PS1^{+/-}/Leva (n $\geq$ 8) mice. Levels of α -tubulin (α -Tub) were used as loading control for normalization purposes. Data are given as a percentage relative to APP/PS1^{+/-} mice. **K-N.** qRT-PCR analysis of *Spp1* (**K**), *P2rx7* (**L**), *Il1b* (**M**), and *Nlrp3* (**N**) mRNA from hippocampus of WT (n = 5), WT/Leva (n = 5), APP/PS1^{+/-} (n = 5) and APP/PS1^{+/-}/Leva (n = 5) mice. Data in box plots represent the distribution of values per group (median, IQR, maximum, and minimum values). # $P \leq 0.08$, * $P \leq 0.05$ or ** $P \leq 0.01$; using a one-way ANOVA followed by Tukey's post hoc test.