

Figure S1.

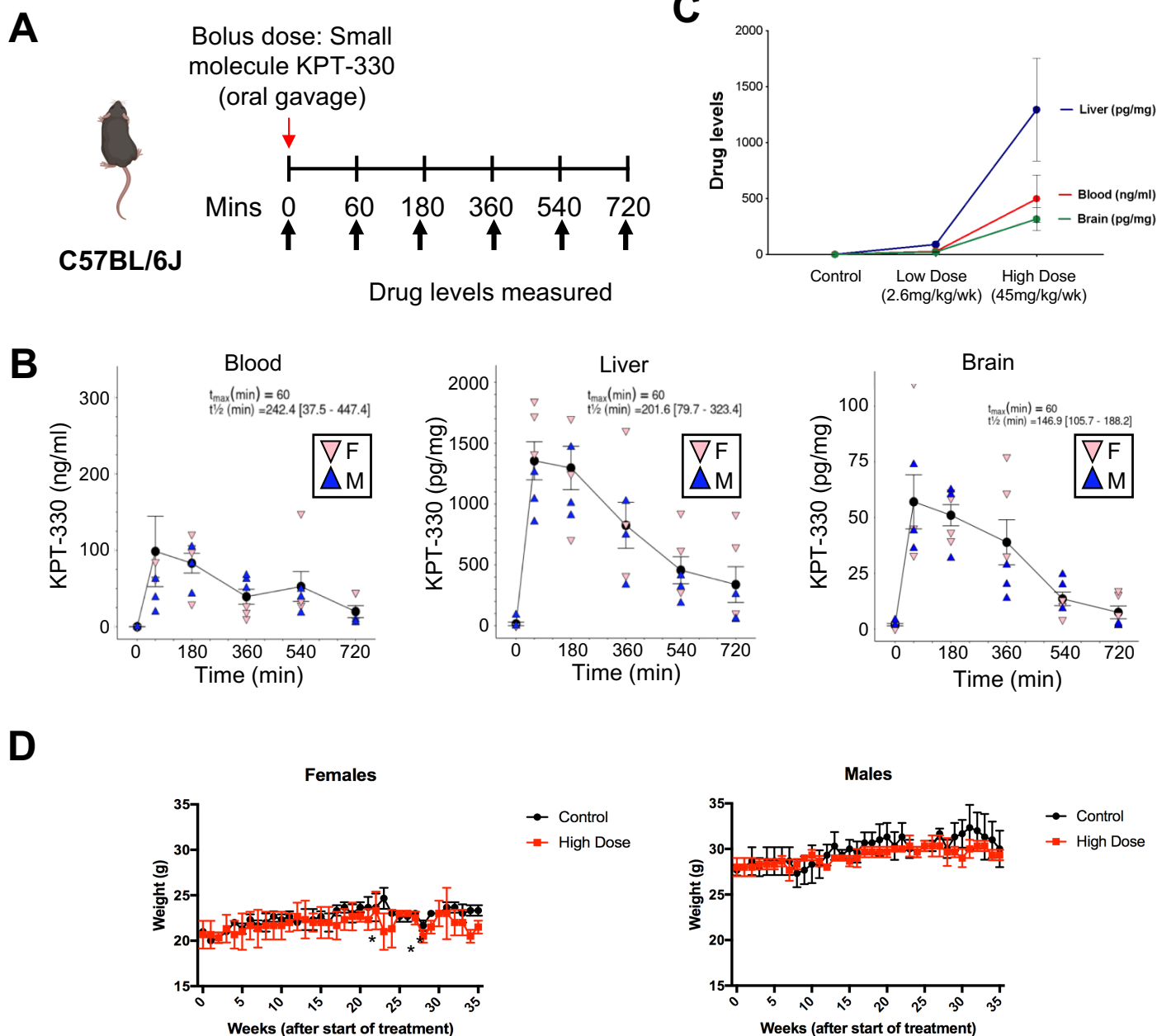


Figure S1. Pharmacological and bioaccumulation analysis of KPT-330. **A.** C57/B6 mice received a bolus dose of 7.5mg/kg KPT-330 (p.o.) and were then sacrificed at 60, 180, 360, 540, and 720 min post administration. **B.** Blood, liver and brain were collected and assessed for KPT-330 concentration in each mouse. At each time point, 4-month old male (n=3) and female (n=3) mice were included. **C.** Blood, liver, and brain levels of KPT-330 were also analyzed in 4-month old mice fed chow, or chow with low or high dose of KPT-330 for two weeks. **D.** Mice weight was measured for the duration of the treatment (45mg/kg/wk) from 4-months to 12 months of age (n=3 per sex per treatment) *: $P < 0.05$, t -test.

Figure S2.

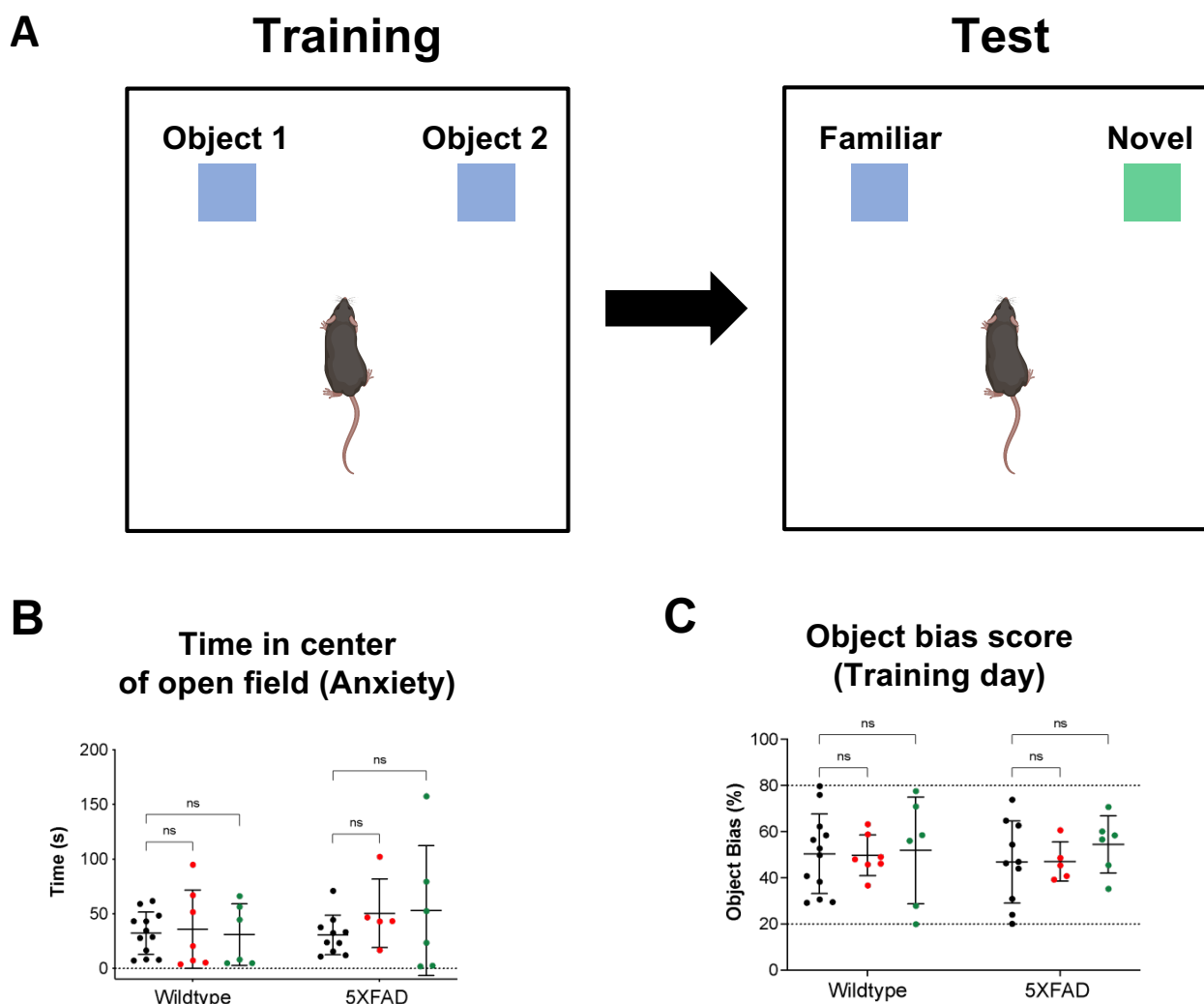
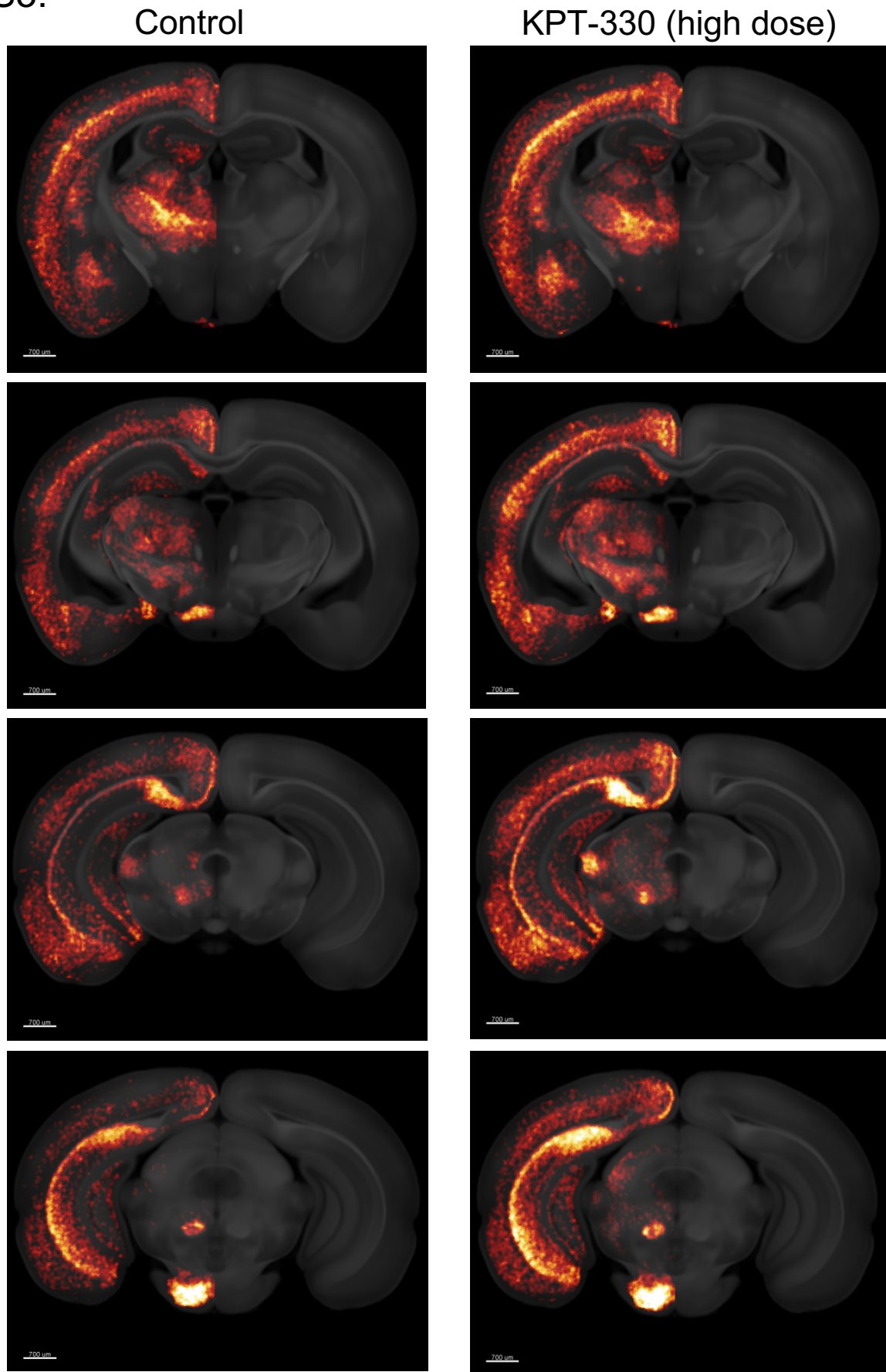


Figure S2. KPT-330 treatment does not improve novel object recognition (NOR) in 5XFAD mice. A. Four-month old wildtype and 5XFAD mice were fed with either chow or chow containing high (45 mg/kg/wk) or low (2.6 mg/kg/wk) dose of the XPO1 inhibitor, KPT-330, for 2 months and assessed for effects on recognition memory using the NOR test at 6 months of age following prior habituation to the test arena and object familiarization (see methods for details). **B.** Time in center of open field and **C.** object bias score during training day were measured. ns: not significant, n=6-12, ANOVA.

Figure S3.



2D planes from average maps

Figure S3. Differential amyloid accumulation in 5XFAD mice brains. Representative 2D images at selected coronal planes showing group average of plaque volume in response to KPT-330 treatment and with control shown in glow scale. Scale bar 700 μ m.

Figure S4.

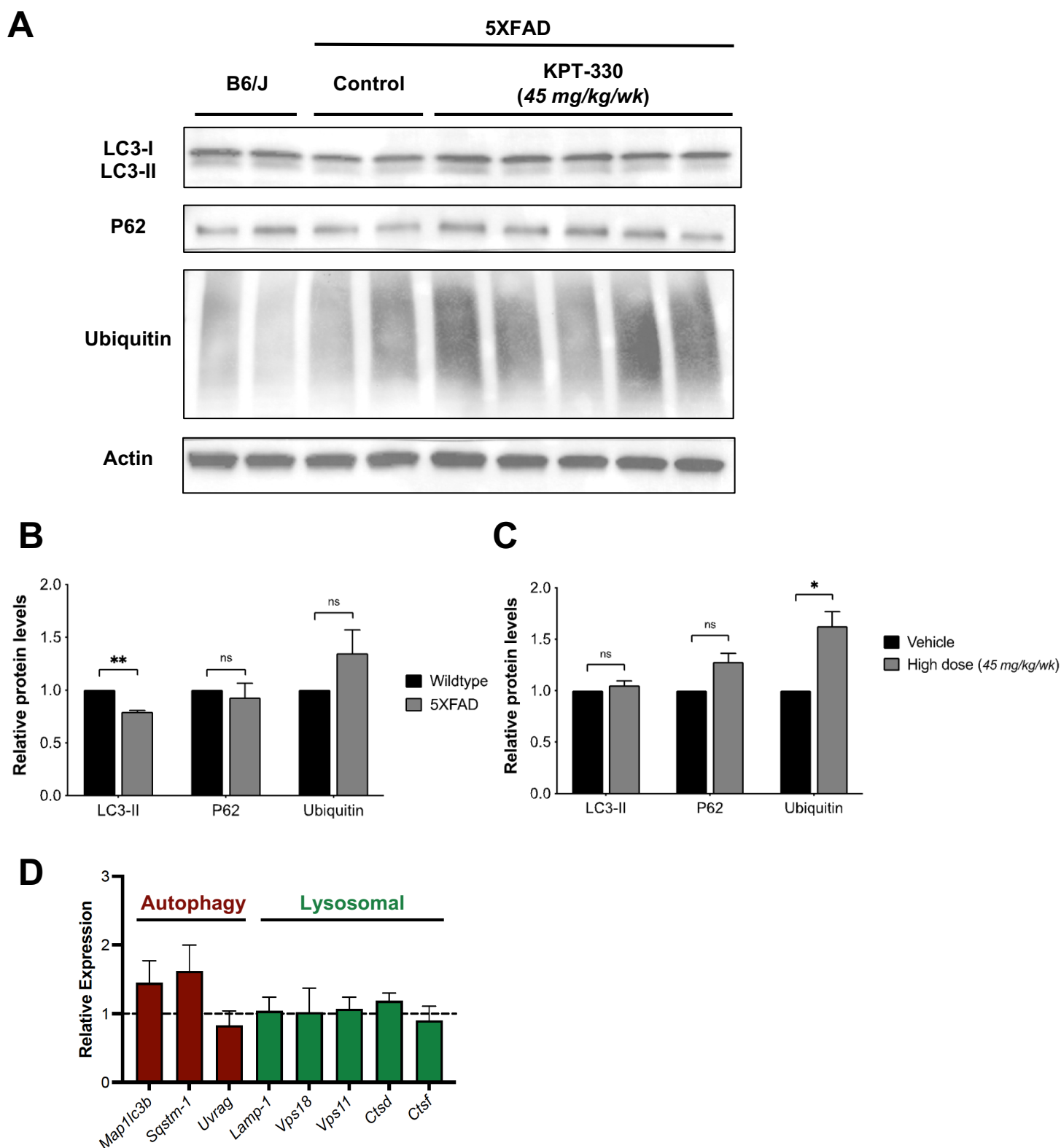


Figure S4. Protein analysis in brains of 5XFAD mice. A. Immunoblotting of LC3, p62 (SQSTM1) and ubiquitin in brains of 9-months old B6/J and transgenic 5XFAD mice (with or without KPT-330 from 4 months of age). **B.** Relative protein levels was compared between B6/J (wild-type) and 5XFAD (**B**) and between control (vehicle) and high dose KPT-330 (**C**). Values expressed as mean of $n = 2 \pm \text{SEM}$; *: $P < 0.05$, **: $P < 0.01$. **D.** mRNA levels of autophagy and lysosomal genes in the brain of 9-month old 5XFAD animals and treated with KPT-330 compared to control (normalized at 1), $n=3$, t -test.

Table S1.

Gene name	Sequence 5' -3'
<i>Gapdh</i> Forward	CATCACTGCCACCCAGAAGACTG
<i>Gapdh</i> Reverse	ATGCCAGTGAGCTTCCCCTTCAG
<i>Actb</i> Forward	GTGACGTTGACATCCGTAAAGA
<i>Actb</i> Reverse	GCCGGACTCATCGTACTCC
<i>B2m</i> Forward	ACCCGCCTCACATTGAAATCC
<i>B2m</i> Reverse	GGCGTATGTATCAGTCTCAGTG
<i>Map11c3b</i> Forward	CGGACTGAGACACACAAGG
<i>Map11c3b</i> Reverse	TCGCTCTATAATCACTGGGATCT
<i>Sqstm1</i> Forward	GGCCTATCTTCTGGGCAAGG
<i>Sqstm1</i> Reverse	CCGGCACTCCTTCTTCTCTTT
<i>Uvrag</i> Forward	ATCCGACGTGGAGGAGTCTT
<i>Uvrag</i> Reverse	TGCGTTTGGATGACCCTTGT
<i>Lamp 1</i> Forward	TGCTCCGGGATGCCACTAT
<i>Lamp 1</i> Reverse	CTTGTTGTCCTTTTTTCAGGTAGGTG
<i>Vps18</i> Forward	CGCCTGCGTCCATGTCTATAA
<i>Vps18</i> Reverse	GGCAGCACATCCTCGATCTT
<i>Vps11</i> Forward	CTGGAAAAGAGAGACGGTGGCAATC
<i>Vps11</i> Reverse	GAAAGGCCAGCCCAGTAACG
<i>Ctsd</i> Forward	CTGTGGGTCCCCTCCATTCATTG
<i>Ctsd</i> Reverse	GGTAGCCCATGCCCAAGATG
<i>Ctsf</i> Forward	CACAGCTCAGTATGGGATCACC
<i>Ctsf</i> Reverse	TTGGCTGGACTCATCTTCTGTC

Table S1. Primer used in the study

Data S1.

See Excel File

Video S1.

See Video File

Video S2.

See Video File