**Supplementary Material**

**Increased Insoluble Amyloid-β Induces Negligible Cognitive Deficits in Old *AppNL/NL* Knock-In Mice**

**Supplementary Fig. 1. No amyloid deposits in the prefrontal cortex from aged *AppNL/NL* mice. A)** Representative images from prefrontal sections from 24-month-old WT or *AppNL/NL* mice stained with Thioflavin. *n*= 4 mice per group. Scale bar represents 200 µm.

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**Supplementary Fig. 2. Morris water maze analysis shows no major cognitive differences between 24-month-old WT and *AppNL/NL* mice.** A, B) Acquisition curve in the Morris water maze test compares the path length (A) and the average velocity (B) during the 10 training days between 24-month-old WT (*n*=10) and *AppNL/NL* (*n*=11) mice. C, D) Time spent swimming in the target quadrant during probe trial 1 (C) (after 5 days of training) and probe trial 2 (D) (after 10 days of training).



**Supplementary Table 1. Correlation analysis between freezing responses in the cued test and Aβ levels.** Table shows the Pearson correlation coefficient and the *p* values for the different Aβ species and the freezing responses during the cued fear test.

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|  | **Pearson r** | **p values** |
| Correlation with soluble Aβ40 | -0.40 | 0.32 |
| Correlation with soluble Aβ42 | -0.28 | 0.50 |
| Correlation with insoluble Aβ40 | -0.35 | 0.40 |
| Correlation with insoluble Aβ42 | -0.43 | 0.29 |