SUPPLEMENTARY INFORMATION

Experimental evidence for temporal uncoupling of brain Aβ deposition and neurodegenerative sequelae

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Supplementary Figures 1-6

Supplementary Table 1

Member List of the Dominantly Inherited Alzheimer Network (DIAN)

a

	APPPS1						WT			
	Bsl		Ctrl		BI		Ctrl		BI	
	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂
Young	7	4	4	6	3	6				
Adult	3	7	5	5	3	6				
Aged	3	7	3	11	3	13				
Young-chronic			4	9	7	8	6	9	7	4
Adult-chronic			13	1	10	2	6	6	7	5

b

Summary of end-point titration

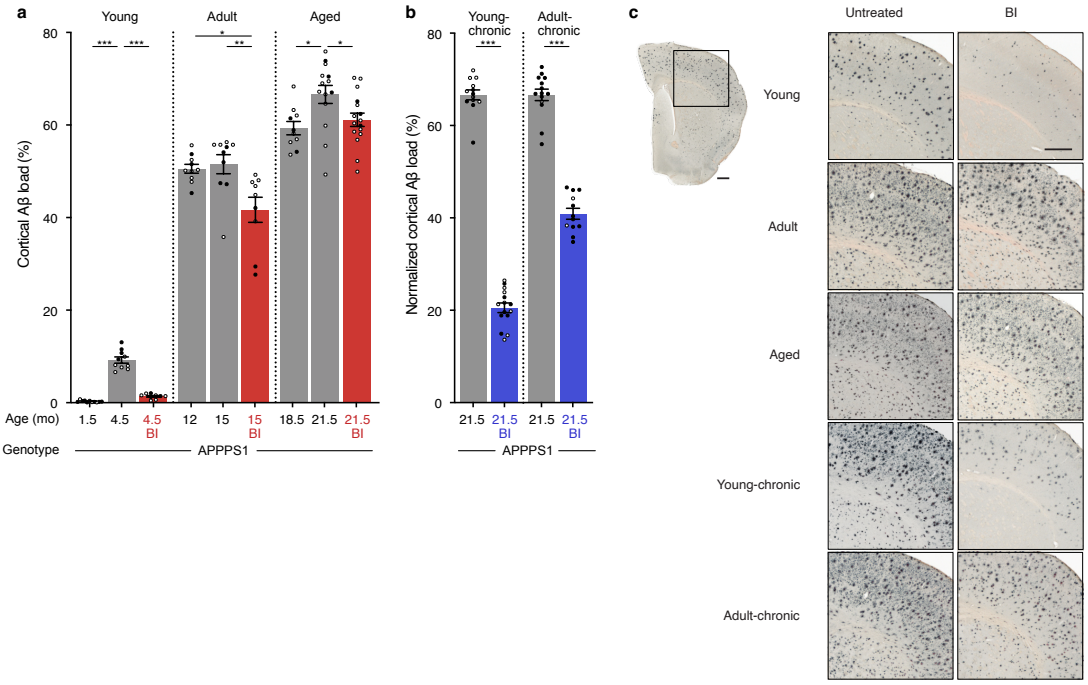
	Number of mice with induced Aβ deposition/ total number of mice inoculated in each group								
dilution	1.2 mo	3 mo	4.5 mo	6 mo	12 mo	15 mo	18 mo	21.5 mo	22 mo
10^{0}	0/5	4/5	-/-	2/2	5/5	-/-	5/5	-/-	3/3
10^{-1}	0/5	5/5	-/-	6/6	4/4	-/-	-/-	-/-	-/-
10^{-2}	-/-	1/5	**3/5**	3/5	3/3	**5/5**	5/5	-/-	4/5
10^{-3}	-/-	-/-	-/-	0/4	0/4	-/-	0/5	**3/5**	1/3
10^{-4}	-/-	-/-	-/-	-/-	-/-	-/-	0/5	-/-	0/5
10^{0}			1/1			1/1		-/- 4/4	
10^{-1}			6/6			5/6		4/5 6/6	
10^{-2}			1/6			4/4		5/5 2/6	
10^{-3}			-/-			-/-		2/5 0/5	

c

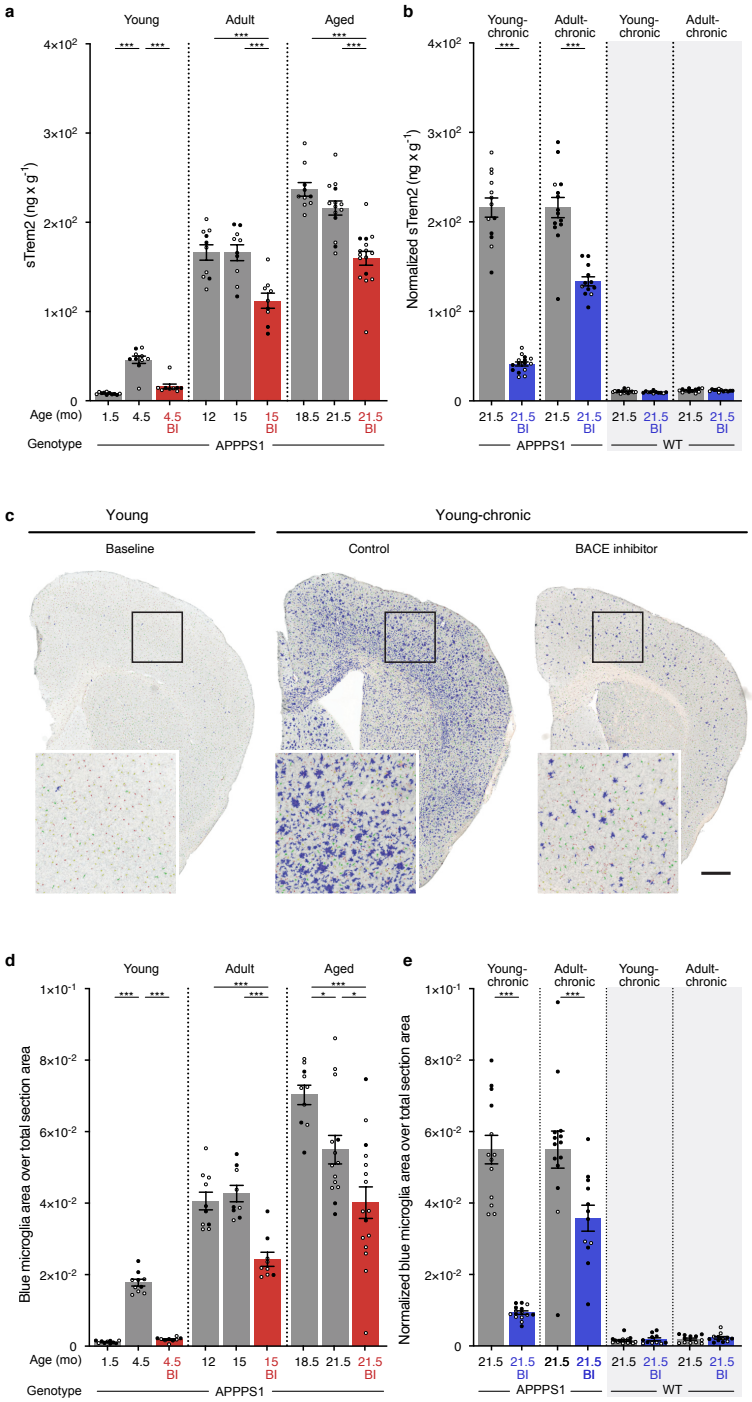
Comparison of SD_{50} calculated for BI-treated APPPS1 mice

	young	adult	aged	young-chronic
Reed-Münch	1.60	2.38	2.83	1.75
Spearman-Kärber	1.67	2.33	2.70	1.83
Curve-fitting	1.58 ± 0.43	2.42 ± 0.3	2.94 ± 0.14	1.76 ± 0.17

Supplementary Figure 1. Number and sex of mice per group. (a) Number of APPPS1 mice and WT mice in the various groups treated with the BACE1-inhibitor (BI), control-treated (Ctrl), or analyzed at baseline (Bsl). See Fig. 1b for group description. The targeted number of mice per group was 10 for the young and adult groups and 12-15 for aged groups (i.e., short-term treatment, aged and chronic treatments). Slight deviations in numbers are the result of mouse availability from our in-house mouse colony or premature death. (Note that there was no difference in deaths between BI- and control-treated mice). Previous research has not revealed an obvious sex difference in CSF NfL or Aβ load inAPPPS1 mice[19,59], and thus both male and female mice were randomly included in the study. **(b)** Number of mice used for the endpoint titration assay to calculate Aβ seeding dose 50 of brain extracts (SD_{50}; see Fig. 3 for details). Shown are the numbers of mice with induced Aβ deposition/total number of mice inoculated per group at each brain extract dilution for the different groups. In the top rows (black) previously published data of untreated APPPS1 mice (number of mice with seeded Aβ deposition/total number of mice in each age group[13]) were incorporated into the present study in line with the 3Rs principles of reducing animal numbers. In bold, animals done in the present study. They were included for comparative analysis with the previously published numbers to make sure that the current and past inoculations results are in the same range. In the bottom rows, the short-term (3 months) BI-treated mice are shown in red while the young-chronic treated mice are shown in blue. Per group, 6-7 mice were inoculated, except for dilutions where seeding could be predicted with high confidence (two dilutions with 1 mouse only). Two groups have only 4 mice due to the death of mice. **(c)** SD_{50} calculations for the BI-treated mice in the present study using three different methods. For curve-fitting the s.e.m. is indicated and curve-fitting was used to generate the curves in Fig. 3c.

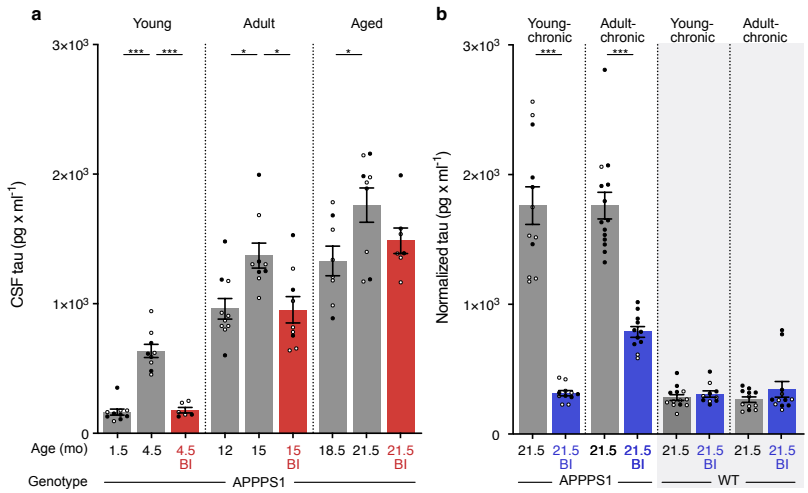


Supplementary Figure 2. Aβ load assessed by immunostaining after short-term and chronic BACE1 inhibition. The same mice were used as in Fig. 2 and outlined in Supplementary Fig. 1a. **(a)** Total Aβ immunostaining in neocortex was determined by stereological analysis, and the results mirror brain Aβ load assessed by the immunoassays shown in Fig. 2a. BI treatment caused a significant decrease in Aβ immunostaining compared to the respective age-matched control group (ANOVA, 'young': $F(2, 27)= 155.8$; 'adult': $F(2, 26)= 7.25$; 'aged': $F(2, 37)= 4.95$; all $P<0.05$; *post hoc* Tukey's multiple comparisons, *P<0.05, **P<0.01, ***P<0.001). **(b)** Cortical Aβ immunostaining in the young-chronic and adult-chronic groups was normalized to the 21.5 mo-old control mice of the 3-month treatment group shown in (b). Two-tailed unpaired *t*-tests show significantly lowered Aβ-immunostaining in both groups ('young chronic': $t(26)=30.99$; 'adult-chronic': $t(24)=14.77$; both ***P<0.001). All data are represented as group means ± s.e.m. Open circles are males, filled circles females; no consistent effect of sex was found (see Methods). (**c**) Representative Aβ-immunostained coronal sections (from sets of every 36th section through the neocortex) for each of the BI-treated and untreated control groups. Scale bars: 500µm.

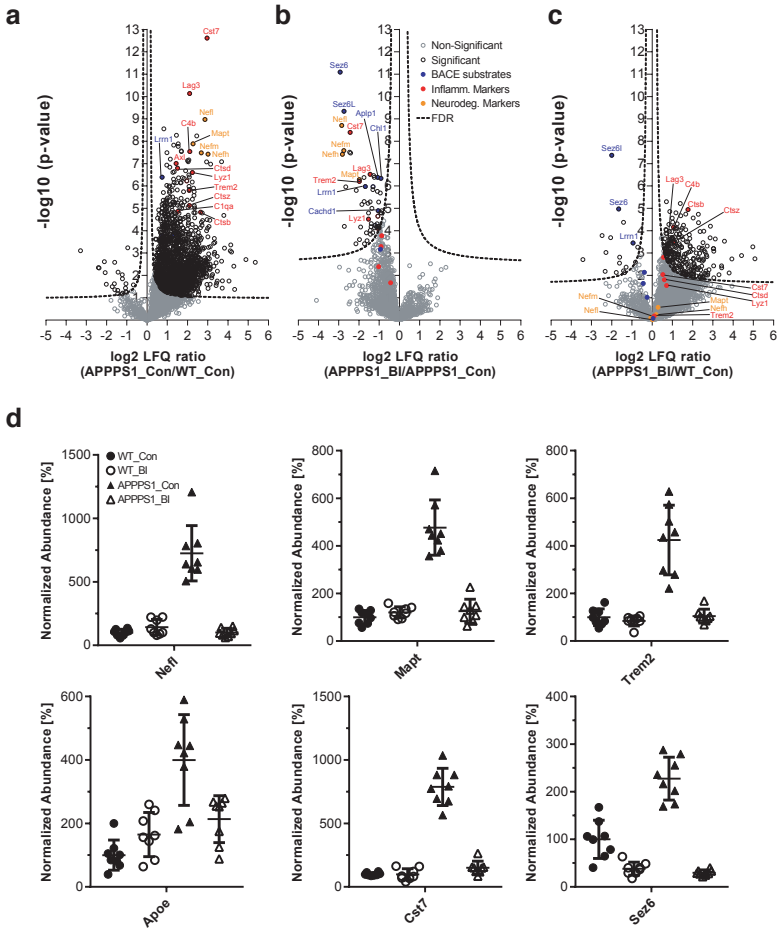


Supplementary Figure 3. Soluble Trem2 and activated microglia after short-term and chronic BACE1 inhibition. The same mice were used as in Fig. 2 and outlined in Supplementary Fig. 1a. **(a, b)** Soluble Trem2 and **(c-e)** microglial activation in brains of APPPS1 and WT mice. **(a)** BI treatment for 3 months caused a significant decrease in soluble Trem2 (sTrem2) compared to the respective age-matched control group, and sTrem2 was below baseline in the 'adult' and 'aged' groups (ANOVA, 'young' ($F(2, 27)= 54.04$; 'adult' $F(2, 26)= 12.25$; 'aged' $F(2, 37)= 25.54$, all $P<0.001$; *post hoc* Tukey's multiple comparisons, ***$P<0.001$). **(b)** Brain sTrem2 in the young-chronic and adult-chronic groups were normalized to the 21.5 mo-old control mice of the 3-month treatment group shown in (a). Two-tailed unpaired *t*-tests revealed significantly lower brain Aβ levels in the BI-treated mice ('young chronic': $t(26)=17.15$; 'adult-chronic': $t(24)=6.229$, both ***$P<0.001$). BI treatment of transgene-negative WT mice had no effect on brain sTrem2. **(c)** Iba1-immunostained microglia in the cortex of APPPS1 and WT mice

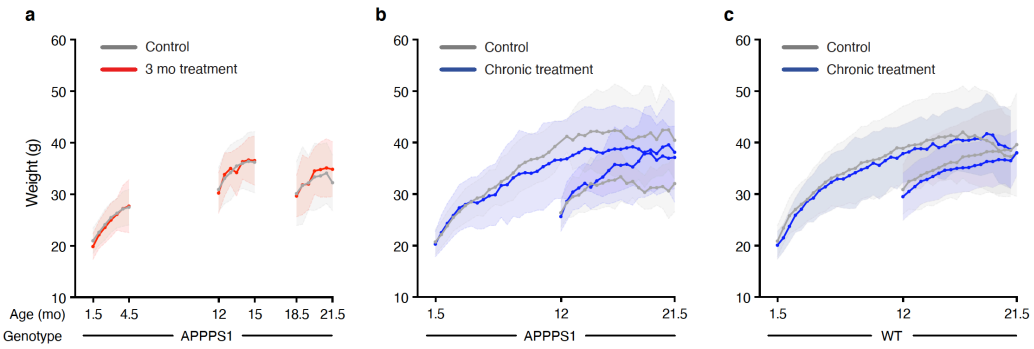
were categorized and colored based on size: Red: area <50μm^2 (resting); yellow: area 50 to < 80μm^2 (resting-intermediate); green: area 80 to <120μm^2 (activated); blue: area ≥120μm^2 (activated, plaque-associated). Representative sections from a 1.5 mo-old APPPS1 mouse (young baseline), two 21.5 mo-old APPPS1mice, one control-treated and one BI-treated mouse from 1.5 mo to 21.5 mo of age. Scale bar insert, 100μm. **(d)** Quantitative analysis revealed a significant decrease of the activated (blue) microglia over the total section area in BI-treated mice compared to controls, and additionally below baseline in the 'adult' and 'aged' groups (ANOVA, 'young' ($F(2, 26)= 279.9$; 'adult' $F(2, 25)= 18.81$; 'aged' $F(2, 37)= 12.85$, all $P<0.001$; *post hoc* Tukey's multiple comparisons, *P<0.05, **P<0.01, ***P<0.001). Note that one 'young baseline' and one 'adult control' mouse were excluded because of a processing error. **(e)** Activated (blue) microglia in the young-chronic and adult-chronic groups were normalized to the 21.5 mo-old control mice of the 3-month treatment group shown in (d). Two-tailed unpaired *t*-tests revealed significantly lower brain Aβ levels in the BI-treated mice ('young-chronic' and 'adult-chronic' $t(26)=12.11$; $P<0.001$ and $t(24)=2.948$; $P=0.0070$, respectively). BI treatment of WT mice had no effect on microglial activation. Note the similarities of the results of sTrem2 and activated microglia to the results for total brain Aβ (Fig. 2 and Supplementary Fig. 2). All data are represented as group means ± s.e.m. Open circles are males, filled circles females; no consistent effect of sex was found (see Methods).



Supplementary Figure 4. CSF Tau after short-term and chronic BACE1 inhibition. CSF Tau was measured at baseline and after short-term BI treatment in 'young', 'adult', and 'aged' mice and after chronic treatments (see Fig. 1 and Supplementary Fig. 1a for treatment groups and number of mice per group – however, note that Tau measurements were performed after CSF NfL and CSF proteome measurements for mice with enough CSF remaining. Accordingly, N was 10, 9, 6 for 1,5 mo, 4.5 mo, and BI 4.5 mo; 10, 9, 9 for 12 mo, 15 mo, and BI 15 mo; 8, 9, 7 for aged 18.5 mo, 21.5 mo, and BI 21.5 mo; 12, 11 for young-chronic 21.5 mo and BI 21.5 mo; 14, 11 for adult-chronic 21.5 mo and BI 21.5 mo; 13, 10 for young-chronic WT 21.5 mo and WT BI 21.5 mo; 12, 12 for adult-chronic WT 21.5 mo and WT BI 21.5 mo). **(a)** BI treatment for 3 months completely prevented the Tau increase (note that in the aged group less than half of the CSF samples were left for analysis (ANOVA, 'young' $F(2, 22) = 56.19$; $P<0.001$; 'adult' $F(2, 25)= 6.664$, $P=0.005$; 'aged' $F(2, 21)= 3.552$, $P=0.05$; *post hoc* Tukey's multiple comparisons, *P<0.05, ***P<0.001. **(b)** CSF Tau levels in the young-chronic and adult-chronic groups were normalized to the 21.5 mo-old control mice of the 3-month treatment group shown in (a). In the adult-chronic group, Tau levels were lowered below baseline (i.e. compared to levels at 12 mo of age) while chronic treatment fully prevented an increase in CSF Tau, given the tau levels in WT mice (two-tailed unpaired *t*-tests for 'young chronic': $t(21)=9.5$; 'adult-chronic': $t(23)=7.973$, both ***P<0.001; 'young chronic WT': $t(21)=0.7996$; 'adult-chronic WT': $t(22)=1.229$, both $P>0.05$). All data are represented as group means ± s.e.m. Open circles are males, filled circles females; no effect of sex was found (see Methods).



Supplementary Figure 5. CSF proteome after chronic BACE1 inhibition. The CSF of the 21.5 mo-old 'young-chronic' (1.5 to 21.5 mo) BI- and control-treated APPPS1 and wildtype (WT) mice was used for proteomic analysis (see Fig. 1 for groups; 8 animals from each group were randomly selected for this proteomic analysis). **(a)** Volcano plot comparing the CSF proteome of control-treated APPPS1 vs. control-treated WT mice (n=8 vs. n=8). Selected proteins are labeled with their UniProt gene names. Note the general increase in the abundance of many neurodegenerative markers (orange) such as Nefl, Nefm, Nefh, and Mapt (Tau) and inflammation-related proteins (red) such as Trem2, Lag3, Ctsz, and Lyz1 in APPPS1 mice compared to WT mice. **(b)** Volcano plot comparing the CSF proteome of 1.5 to 21.5 mo BI-treated vs. control-treated APPPS1 mice (n=8 vs. n=8) demonstrate that long-term BI treatment largely prevents the changes shown in (a). **(c)** Volcano plot comparing chronic (life-long) BI-treated APPPS1 mice vs. control-treated WT control mice (n=8 vs. n=8). The significant reduction of the well-known BACE1 substrates (blue) such as Sez6 and Sez6l validates the successful BACE inhibition until old age. For all Volcano plots the –log10 of the p-value of each protein is plotted against its log2 fold difference for each group comparison. The hyperbolic curves indicate the thresholds of the permutation-based FDR correction for multiple hypotheses (p=0.05; s_0=0.1). Proteins above the FDR curves (black circles) are significantly changed. **(d)** Dot plots of selected proteins. The protein LFQ intensities were normalized on the average of the WT control-treated mice (mean and SD). Note again the increase of Nefl and Mapt, and the neuroinflammatory markers sTrem2, Apoe, and Cst7 in APPPS1 mice, as well as the near complete normalization of the values by BACE inhibition. The well-known BACE substrate Sez6 shows a decreased abundance due to BACE inhibition in both WT and APPPS1 mice, validating the efficacy of BACE1 inhibition into old age. For detailed proteomic results see Supplementary Data 1.



Supplementary Figure 6. Weekly body weights of BACE1-Inhibitor- and control-treated APPPS1 and wildtype mice. See Fig. 1b for group description and Supplementary Fig. 1 for mouse numbers. **(a)** No difference in body weight was observed in any of the three age groups of APPPS1 mice treated for 3 months with BI vs. control treatment. Note that, in the 'aged' 18.5 – 21.5 mo-old group, seven longitudinal datasets were incomplete. **(b, c)** Body weight of chronically treated young and adult APPPS1 mice (b) or non-transgenic WT mice (c). While BI treatment had no robust effect on body weight in the WT mice, apparent opposite changes, depending on the start of the treatment, were noted in the APPPS1 mice. Shown are group means ± SD (shaded area). Note that the BI-containing food pellets and control pellets (same pellets without the BI) were more nutritious compared to the standard lab chow, and thus animals tended to gain weight when switched to the BI-containing food pellets and control pellets.

CSF NfL [pg/mL] in	**Age group**					
	1.5 mo	**3 mo**	**6 mo**	**12 mo**	**18 mo**	**end-stage**
APPPS1	**63** ±3.4 (n=3)	**410** ±30.8 (n=9)	**1,255** ±85.8 (n=10)	**3,405** ±354 (n=12)	**12,475** ±1,446 (n=11)	**19,689** ±1,566 (n=9)
	61	529	1,170	4,227	5,775	23,562
	58	505	1,330	2,078	14,986	25,004
	69	318	1,491	2,727	9,559	21,252
		416	981	4,466	22,464	18,015
		510	1,631	4,718	9,573	15,134
		428	1,568	2,926	14,467	14,252
		278	1,407	2,415	10,031	14,084
		2,583	1,103	1,512	16,296	19,404
		379	1,053	3,402	6,727	26,495
		323	816	5,474	14,588	
				4,383	12,754	
				2,526		
	1.5 mo	**3 mo**	**6 mo**	**12 mo**	**18 mo**	**end-stage***
WT	**169** ±7.9 (n=3)	**239** ±27.2 (n=6)	**438** ±68.9 (n=3)	**623** ±57.4 (n=7)	**1,290** ±187.4 (n=6)	**5,903** ±1,171 (n=6)
	155	318	374	606	1,016	11,207
	171	162	575	365	926	6,566
	182	226	364	651	1,070	4,571
		190		603	974	4,935
		217		2,025	1,931	5,327
		322		888	1,825	2,814
				608		
				642		

Mean ±SEM (grey values: significant outliers according to Grubb's test; P<0.05)

* Since the mean age of the end stage WT group was 26 months compared to 22 months in the APPPS1 mice, the mean value of CSF NFL for 22-mo-old WT mice was interpolated (2,756 pg/mL) based on polynomial curve-fitting (4th degree).

Supplementary Table 1. CSF NfL values of APPPS1 mice and wildtype (WT) mice used to generate the curve in Fig. 1a.

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