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Supplementary information

Myelin dysfunction drives amyloid-β deposition in models of Alzheimer's disease

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Supplementary Information Figure legends

SI Figure 1. Source data for western blot analysis
(a-j) Uncropped Western blot raw data. Molecular weight marker is indicated

on the left (given in kDa). Red boxes indicate cropped regions as presented in the figures and the extended data figures. For normalisation, fast green total protein staining was performed on the same blot. Corresponding figure /extended data figure is indicated above each blot.

SI Figure 2. Myelination and gliosis in myelin mutant and aged mice (SI for Extended Data Figures 1d).

(a) Raw data shown as heatmap in Extended Data Figure 1 d. The percentage a rea positive for immunostaining (MBP for myelin profiles, GFAP for astrogli osis and IBA1 for microgliosis) was quantified in the indicated ROIs. m: mo nths. Bars represent means; dots represent individual mice/biological repli cate/n (n=3 per group). Statistical analysis: ordinary one-way ANOVA (p-val ue is given in graphs).

(b) Results of Tukey's posthoc test for all comparisons after ordinary one -way ANOVA on data shown in (a).

SI Figure 3. Assessment of *in toto* amyloid burden by light sheet microscopy.

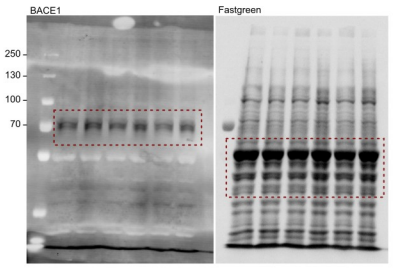
(I) Brains were subjected to *in toto* staining with the β-sheet dye Cong o Red according to a modified iDisco protocol (see Material and Methods) fo llowed by clearing in Ethylcinnamate (Eci).

(II) Cleared brains were imaged on an Ultramicroscope II (LaVision-Biotech) light sheet setup to obtain sagittal optical slices.

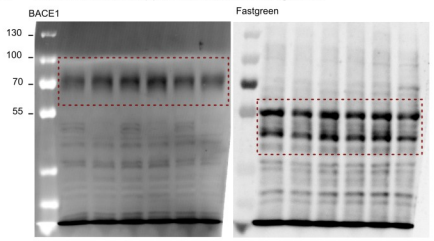
(III) Raw data were visualised and analysed in Arivis Vision 4D using manua l region of interest annotation for hippocampus and cortex and automated pl aque segmentation (intensity-thresholding: 3-month-old *5xFAD*, blobfinder al gorithm: 6-month-old *5xFAD*, machine learning: 6-month-old App^{NLGF}).

Supplementary Figure 1

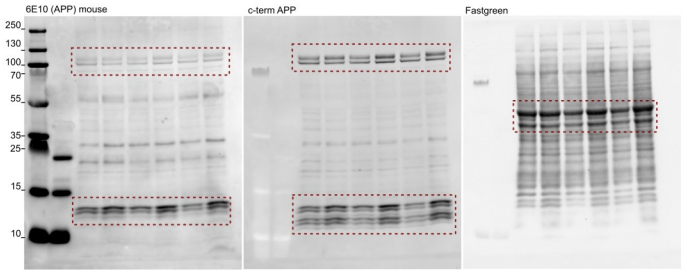
a Western Blot uncropped Main Figure 3f



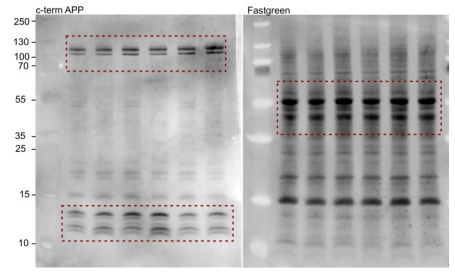
b Western Blot uncropped Extended Data Figure 6l



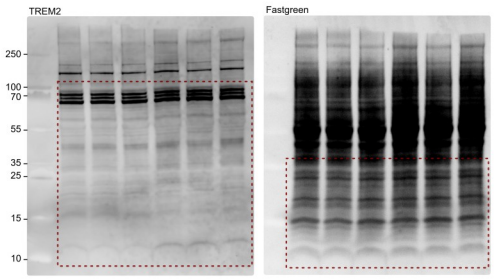
c Western Blot uncropped Main Figure 3g and Extended Data Figure 6m



d Western Blot uncropped Extended Data Figure 6n



e Western Blot uncropped Extended Data Figure 10a



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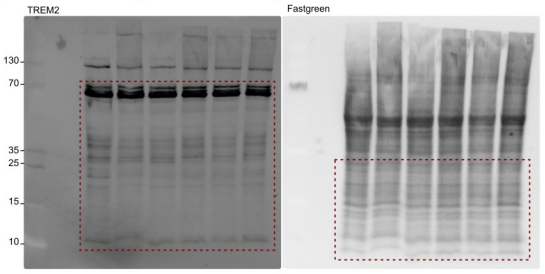
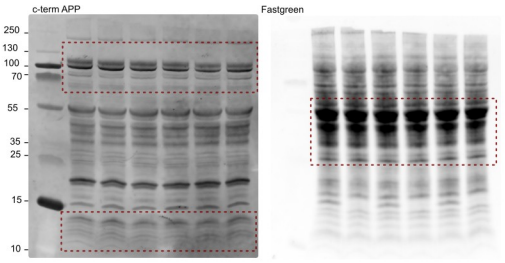
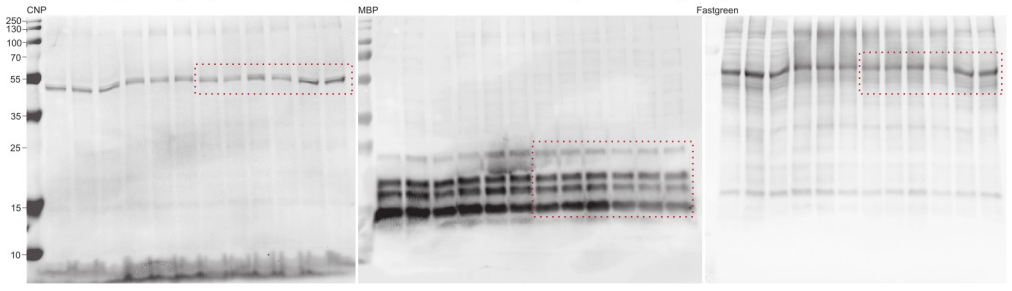


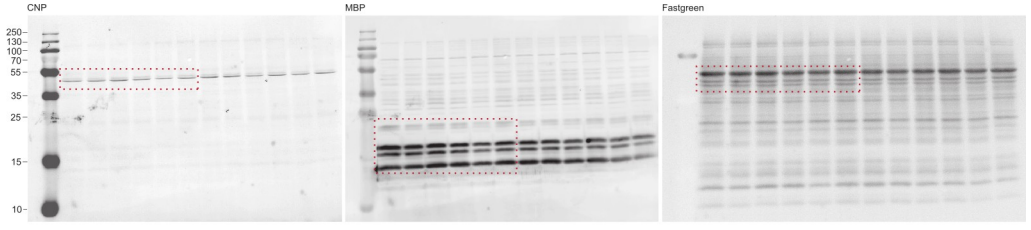
g Western Blot uncropped Extended Data Figure 10g



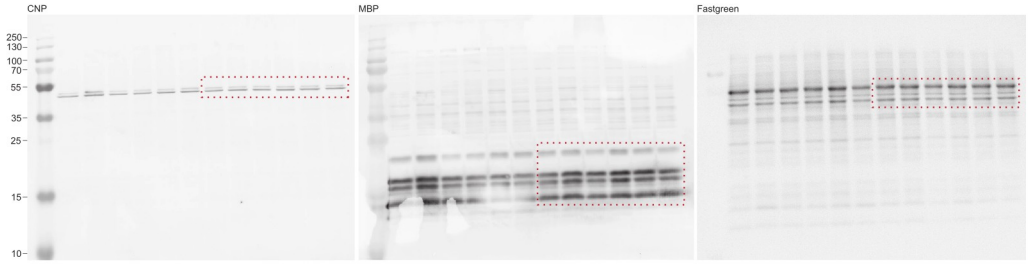
h Western Blot uncropped for myelin proteins in whole hemispheres of WT, 5xFAD, and NLGF mice (Extended Data Figure 3d)



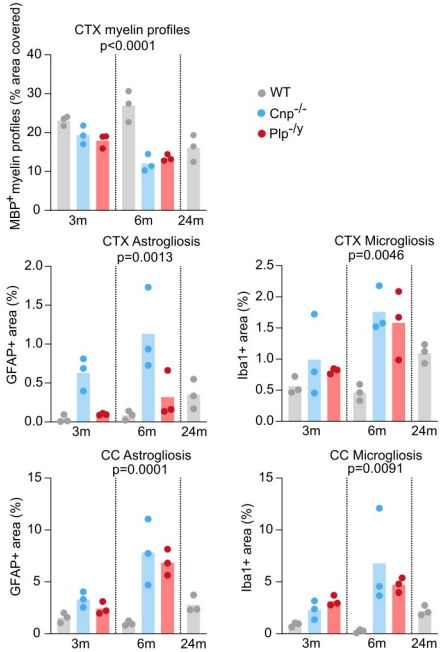
i Western Blot uncropped for myelin proteins in cortical fractions of WT, 5xFAD, and NLGF mice (Extended Data Figure 3d)



j Western Blot uncropped for myelin proteins in hippocampal fractions of WT, 5xFAD, and NLGF mice (Extended Data Figure 3d)



a Quantification of gliosis and myelin contant in myelin mutants



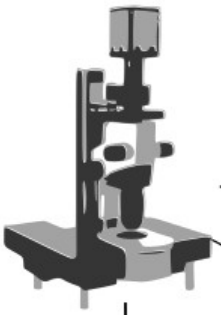
b Statistical analysis

		CTX		CC	
Comparisons	Myelin	GFAP	Iba1	GFAP	Iba1
WT 6m vs. $Cnp^{-/-}$ 6m	<0.0001	0.0027	0.0092	0.0005	0.0087
WT 6m vs. $Plp^{-/y}$ 6m	0.0002	0.9075	0.0274	0.0021	0.1031
WT 6m vs. WT 24m	0.0016	0.8504	0.3925	0.6962	0.8357
WT 6m vs. WT 3m	0.5245	>0,9999	0.9998	0.9986	0.9994
WT 6m vs. $Cnp^{-/-}$ 3m	0.0291	0.1898	0.5856	0.4384	0.8052
WT 6m vs. $Plp^{-/y}$ 3m	0.0083	>0,9999	0.8965	0.8561	0.4881
$Cnp^{-/-}$ 6m vs. $Plp^{-/y}$ 6m	0.9903	0.0211	0.9959	0.9728	0.8021
$Cnp^{-/-}$ 6m vs. WT 24m	0.4646	0.0275	0.3413	0.0077	0.0914
$Cnp^{-/-}$ 6m vs. WT 3m	0.0013	0.0018	0.0171	0.0011	0.0188
$Cnp^{-/-}$ 6m vs. $Cnp^{-/-}$ 3m	0.0369	0.2675	0.2054	0.0175	0.102
$Cnp^{-/-}$ 6m vs. $Plp^{-/y}$ 3m	0.1227	0.003	0.0753	0.0044	0.2516
$Plp^{-/y}$ 6m vs. WT 24m	0.8497	>0,9999	0.6681	0.0368	0.6343
$Plp^{-/y}$ 6m vs. WT 3m	0.0047	0.8163	0.0504	0.0051	0.2057
$Plp^{-/y}$ 6m vs. $Cnp^{-/-}$ 3m	0.1255	0.7439	0.467	0.0818	0.6716
$Plp^{-/y}$ 6m vs. $Plp^{-/y}$ 3m	0.3564	0.928	0.2024	0.0208	0.9303
WT 24m vs. WT 3m	0.0476	0.7404	0.579	0.9203	0.9687
WT 24m vs. $Cnp^{-/-}$ 3m	0.6839	0.8193	0.9998	0.9991	>0,9999
WT 24m vs. $Plp^{-/y}$ 3m	0.9642	0.8776	0.9557	0.9999	0.9946
WT 3m vs. $Cnp^{-/-}$ 3m	0.5447	0.1329	0.777	0.7164	0.9566
WT 3m vs. $Plp^{-/y}$ 3m	0.2205	>0,9999	0.978	0.9835	0.7322
$Cnp^{-/-}$ 3m vs. $Plp^{-/y}$ 3m	0.9912	0.2101	0.9955	0.9849	0.997

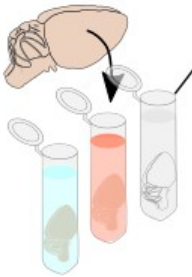
Protocol *in toto* amyloid plaque burden

Light Sheet Microscopy

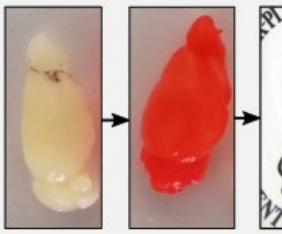
Ultramicroscope II



modified iDISCO

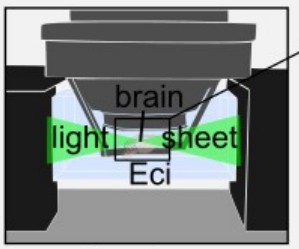


(I)

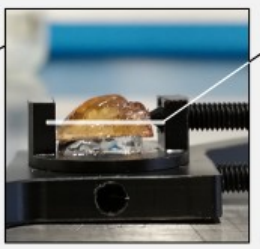


CongoRed MeOH/Eci clearing

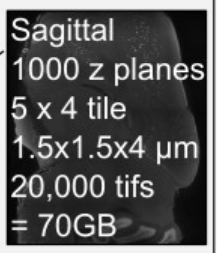
(II)



Imaging



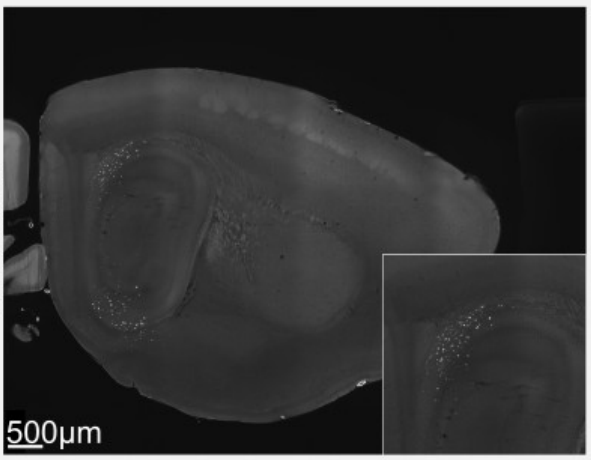
Insertion



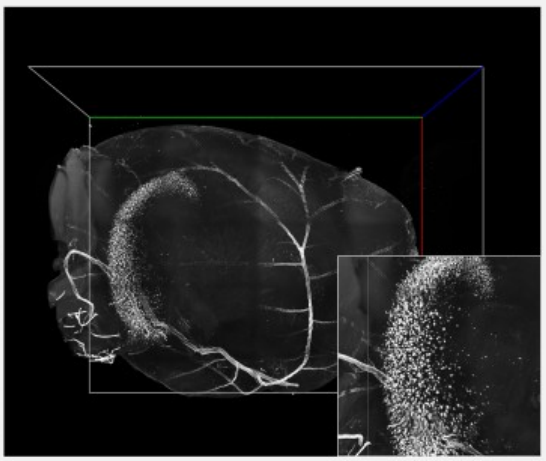
Raw data

Data analysis

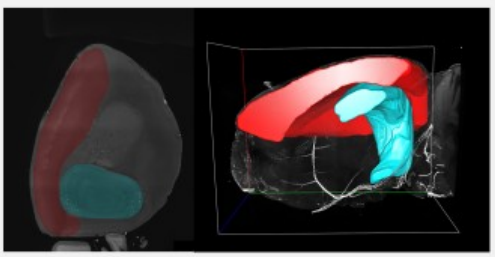
(III)



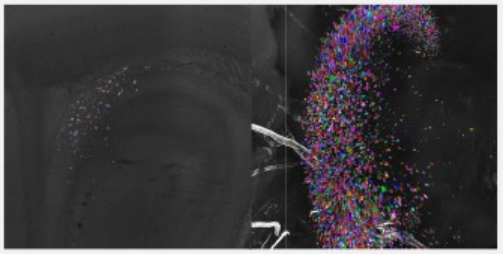
2D view



3D view



2D/3D anatomical annotation



intensity-based segmentation