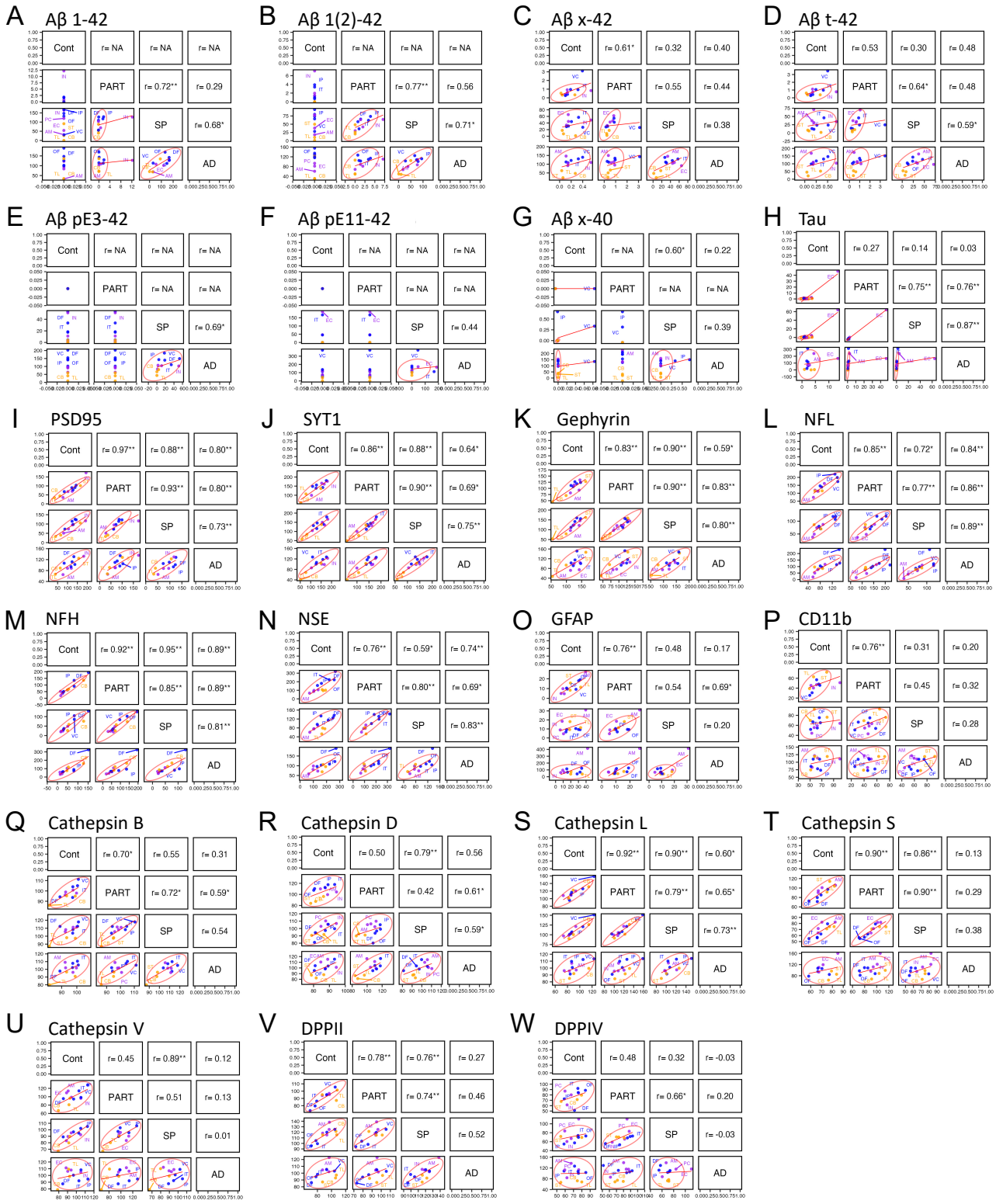
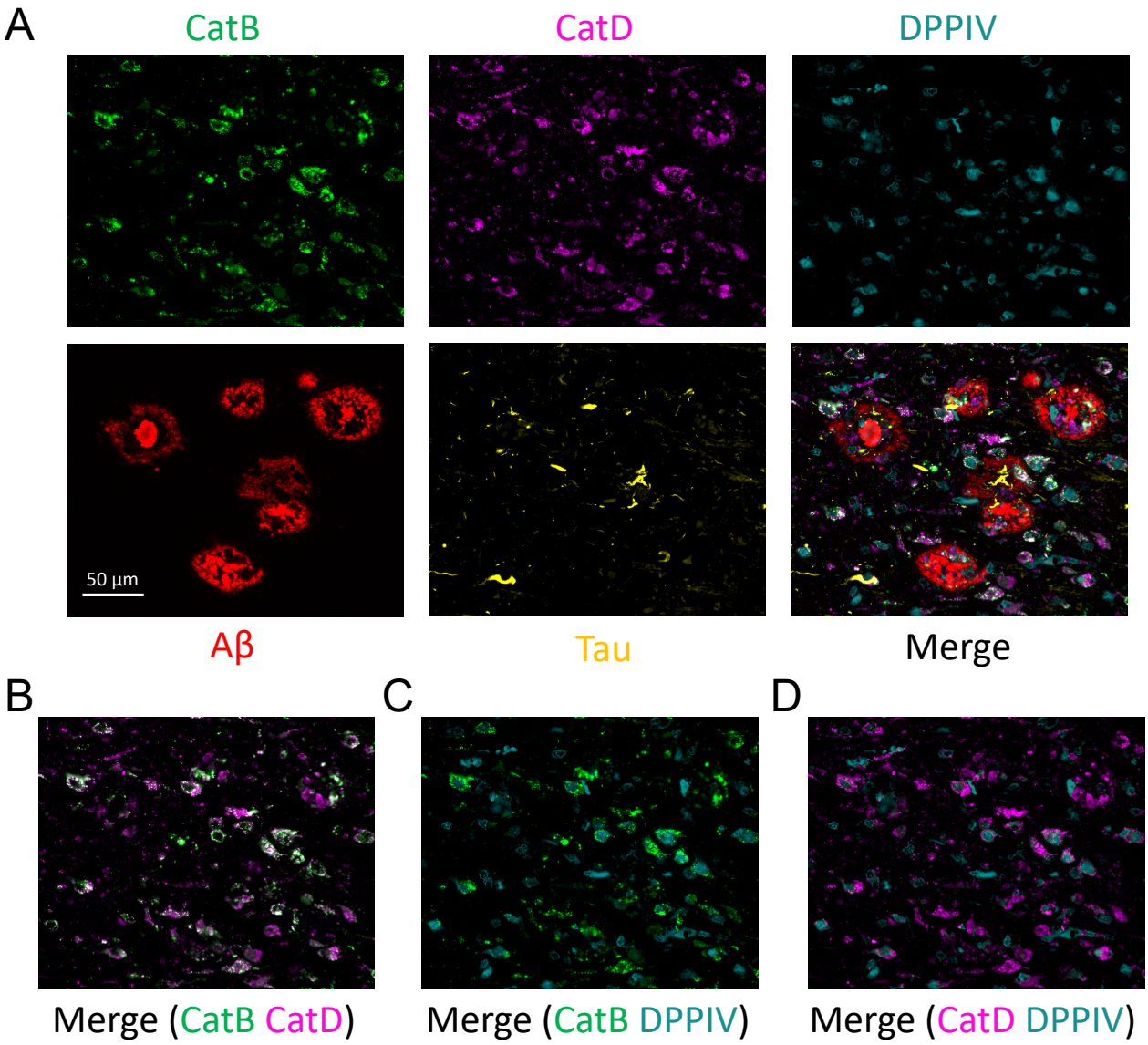


Supplementary Figure 1. Regional association among each four groups of $A\beta_{1\text{-}42}$ (A), $A\beta_{1(2)\text{-}42}$ (B), $A\beta_{x\text{-}42}$ (C), $A\beta_{t\text{-}42}$ (D), $A\beta_{pE3\text{-}42}$ (E), $A\beta_{pE11\text{-}42}$ (F), $A\beta_{x\text{-}40}$ (G), tau (H), PSD95 (I), SYT1 (J), gephyrin (K), NFL (L), NFH (M), NSE (N), GFAP (O), and CD11b (P), cathepsin B (Q), cathepsin D (R), cathepsin L (S), cathepsin S (T), cathepsin V (U), DPPII (V), and DPPIV (W) are shown as scatterplot matrix panels. Lower panels show the scatter plot of average values of each region with a linear regression line and 95% confidence ellipse, and upper panels show its correlation values, by the combination of corresponding diagonal panel variables. *$p < 0.05$ and **$p < 0.01$. Correlation coefficient (r) and p-values were acquired by the Pearson correlation test. The blue notation indicates neocortical areas (DF, OF, IT, IP, and VC); the purple notation indicates limbic areas (PC, EC, AM, and IN); and the orange notation indicates subcortical areas (ST, TL, and CB).



Supplementary Figure 2. Regional associations between neuro-glial markers and cathepsins or dipeptidyl peptidases. Scatter plots of average values of each region with a linear regression line and 95% confidence ellipse by the combination of corresponding top and right panel variables. Small rectangles in each panel show correlation values. The green notation indicates control group, the yellow notation indicates PART group, the cyan notation indicates SP group, and the red notation indicates AD group. *; $p < 0.05$ and **; $p < 0.01$. Correlation coefficients (r) and p-values were acquired by the Pearson correlation test.



Supplementary Figure 3. (A) Fluorescent staining of the dorsolateral frontal cortex of an AD case using an anti-cathepsin B antibody (green), anti-cathepsin D antibody (magenta), anti-DPPIV antibody (cyan), anti-Aβ antibody (4G8, red), and anti-tau antibody (GT-38, yellow) (individual channel images of Fig. 6). (B-D) Merged images of (B) the green channel (cathepsin B) and the magenta channel (cathepsin D), (C) the green channel (cathepsin B) and the cyan channel (DPPIV), or (D) the magenta channel (cathepsin D) and the cyan channel (DPPIV). The scale bar represents 50 µm.

Supplementary Table 1. Demographic characteristic of the four groups.

	Control	PART	SP	AD	p-value
Number	5	4	4	5	-
M:F	4:1	2:2	3:1	3:2	0.7683
Age (y)	74.2 ± 10.4	87.5 ± 12.8	83.3 ± 4.4	84.2 ± 6.1	0.1778
PMI (h)	11.1 ± 8.6	17.0 ± 10.5	7.9 ± 5.3	9.7 ± 8.6	0.4891
APOE (E3/E3: E3/E4: E4/E4)	4:1:0	4:0:0	2:2:0	1:2:2	0.0786
Braak SP score	0 (0-0)	0 (0-1)	3 (2-3)	3 (3-3)	<0.0001
Braak NFT stage	1 (1-1)	3 (3-4)	2 (2-4)	6 (5-6)	<0.0001
CDR score	0	0.5 (0-1)	0 (0-0.5)	3 (2-3)	<0.0001

Values are mean ± SD (range) for age, and PMI. Values are median (range) for Braak senile plaque (SP) score, Braak NFT stage, and CDR.

P-values were acquired by one-way ANOVA (numerical data) or chi-square test (categorical data). Braak SP scores (A–C) were treated as numeric values (1–3). Braak NFT stages (I–VI) were treated as numeric values (1–6). M = male, F = female, PMI = post mortem interval, CDR = clinical dementia rating

Supplementary Table 2. Details of ELISA antibodies or kit used in the current study.

Target	Capture antibody			Detection antibody				2nd Detection Reagent	Standard	Ref
	Name	Host	Source/Cat#	Name	Host	Source/Cat#	Modification			
Aβ1-42	2.1.3 (x-42 specific)	Ms	Mayo Clinic	82E1 (1-x specific)	Ms	IBL/#10323	biotin-linked	HRP Avidin-D	1-42 peptides (AS-20276, SnaSpec)	
Aβ1(2)-42	2.1.3 (x-42 specific)	Ms	Mayo Clinic	Ab5 (1-x or 2-x specific)	Ms	Mayo Clinic	biotin-linked	HRP Avidin-D	1-42 peptides (AS-20276, SnaSpec)	[1-3]
AβX-42	2.1.3 (x-42 specific)	Ms	Mayo Clinic	4G8 (17-24)	Ms	BioLegend/800709	biotin-linked	HRP Avidin-D	1-42 peptides (AS-20276, SnaSpec)	
Aβ p E3-42	2.1.3 (x-42 specific)	Ms	Mayo Clinic	N3pE (pE3-x specific)	Rb	IBL/#18591	–	Anti-rabbit HRP conjugate	pE3-42 peptides (4367-v, Peptide Institute)	
Aβ p E11-42	2.1.3 (x-42 specific)	Ms	Mayo Clinic	Abeta-pE11 antibody	Rb	Synaptic Systems/ 218603	biotin-linked	HRP Avidin-D	pE11-42 peptides (AS-29903, AnaSpec)	[3]
AβX-40	1A10 (x-40 specific)	Ms	IBL/#10047	4G8 (17-24)	Ms	BioLegend/800709	biotin-linked	HRP Avidin-D	1-40 peptides (4307-v, Peptide Institute)	
Tau	Rabbit antibody to Tau	Rb	Osenses/OST00329W	77G7 (316-355)	Ms	BioLegend/816701	biotin-linked	Streptavidin-PolyHRP40	Recombinant Tau-441 (205-20331, Wako)	[4]
PSD95	Rabbit antibody to PSD95	Rb	Osenses/OSD00037W	K28/43	Ms	BioLegend/810401	biotin-linked	HRP Avidin-D	Recombinant PSD95 (LS-G39803, LSBio)	[1-3]
SYT1	Anti-Synaptotagmin1/2 cytoplasmic tail	Rb	Synaptic Systems/105 002	Anti-Synaptotagmin1 cytoplasmic tail	Ms	Synaptic Systems/105 011BT	biotin-linked	HRP Avidin-D	Recombinant SYT1 (TP327252, OriGene)	[5]
Gephyrin	Rabbit antibody to Gephyrin	Rb	Osenses/OSG00053W	Gephyrin antibody	Ms	Synaptic Systems/147 111BT	biotin-linked	HRP Avidin-D	Recombinant Gephyrin (TP305986, OriGene)	
NF-L	7D1	Ms	LSBio/LS-C204557-100	C28E10	Rb	Cell signaling technology/2837BF	–	Anti-rabbit HRP conjugate	Purified Neurofilament 70 (AG231, Millipore)	
NF-H	SMI 35	Ms	BioLegend/835601	Anti-Neurofilament 200	Rb	Sigma Aldrich/N4142	–	Anti-rabbit HRP conjugate	Purified Neurofilament 200 (62210, Progen)	[5]
GFAP	Anti-GFAP	Rb	US Biological/G2032-27J	GA5	Ms	Abcam/ab79203	biotin-linked	HRP Avidin-D	Recombinant GFAP (H00002670-P01, Abnova)	[1-3]
CD11b	M1/70	Rat	Bio X Cell/BE0007	5C6	Rat	Bio RAD/MCA711G	biotin-linked	HRP Avidin-D	Rebombinant CD11b (4047-AM-050, R&D)	[4]
Cathepsin D	Anti-CTSD	Rb	US Biological/125465	Human Cathepsin D Antibody	Goat	R&D Systems/AF1014	biotin-linked	HRP Avidin-D	Recombinant CTSD (1014-AS-010, R&D)	
NSE	Commercial ELISA kit (DY5169-05, R&D Systems)									
Cathepsin B	Commercial ELISA kit (DY2176, R&D Systems)									
Cathepsin L	Commercial ELISA kit (DY952, R&D Systems)									
Cathepsin S	Commercial ELISA kit (DY1183, R&D Systems)									
Cathepsin V	Commercial ELISA kit (DY1080, R&D Systems)									
DPPII	Commercial ELISA kit (DY3438-05, R&D Systems)									
DPPIV	Commercial ELISA kit (DY1180, R&D Systems)									

Ms = mouse, Rb = Rabbit

ELISA procedure

96-well microplates (MaxiSorp, #442404, Thermo Fisher) were coated overnight at 4 °C with 100 µl of capture antibody solution (listed above) at appropriate concentration (typically, 1-2 µg/ml) or appropriate dilution in carbonate-bicarbonate buffer (pH 9.6) containing 0.02% NaN_3. After discarding the coating solution, the wells were blocked with 150 µl of 1% Block Ace (# UK-B80, DS Pharma Biomedical Co, Japan) in PBS containing 0.05% NaN_3 for 2 h at room temperature. After washing with PBS three times, 100 µl of appropriately diluted samples or standards were added to wells containing 50 µl of EC buffer (0.02 M phosphate buffer, pH 7.0, containing 0.4 M NaCl, 2 mM EDTA, 0.4% Block Ace, 0.2% BSA, 0.05% CHAPS [3-[(3-Cholamidopropyl) dimethylammonio]-1-propanesulfonate], and 0.05% NaN_3) and incubated overnight at 4 °C. For the detection antibody, a buffer was prepared by mixing EC buffer and 0.2% BSA–TBS in a 1:2 ratio, and the antibody (listed above) was diluted in this buffer. After washing with PBS-T (0.05% Tween-20 in PBS) five times, 100 µl of appropriately diluted detection antibody were added, and incubated for 2 h at room temperature. After washing with PBS-T five times, 100 µl of appropriately diluted horseradish peroxidase (HRP) Avidin-D (#A2004, Vector Laboratories, Burlingame, CA, USA), streptavidin-PolyHRP40 (#SP40C, Stereospecific Detection Technologies, Baesweiler, Germany), or anti-rabbit HRP conjugate (#W401B, Promega, Madison, WI, USA) in C buffer (0.02M phosphate buffer, pH7.0, containing 0.4 M NaCl, 2 mM EDTA, and 1% BSA) were added to wells, and incubated for 90 min at room temperature. After washing with PBS-T five times, 100 µl of 3,3',5,5'-tetramethylbenzidine substrate solution (#T2885, Sigma-Aldrich) was added, and the reaction was stopped by by adding 100 µl of 1 M phosphoric acid solution. Absorbance at 450 nm was measured using an iMark plate reader (BIO-RAD, Hercules, CA, USA).

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