Supplementary Information

CSF synaptic proteins demonstrate region-wise associations with cerebral amyloid burden

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Supplementary Methods

1. PET acquisition and reconstruction

AV-45 was administered as a single intravenous bolus injection via a peripheral venous catheter in the forearm, followed by a saline flush to ensure complete tracer delivery. Imaging data were acquired 50–70 minutes post-injection according to ADNI protocols.[1] PET data were acquired on ADNI-qualified PET/computed tomography (CT) scanners from multiple vendors (GE, Siemens, and Philips) in accordance with ADNI protocols.[1] Images were reconstructed using scanner-specific iterative algorithms (ordered-subsets expectation maximization or equivalent), with vendor-defined numbers of iterations and subsets, and were corrected for attenuation, scatter, randoms, and dead time as specified in the ADNI PET Technical Procedures Manual. PET data were reconstructed as four consecutive frames spanning 3000–4200 s post-injection, each with a duration of 5 minutes of acquisition time.

2. Image format conversion

Image data were converted to Neuroimaging Informatics Technology Initiative (NIfTI) format using format-specific pipelines. Digital imaging and communications in medicine (DICOM) images were converted using 'dcm2niix' (MRIcroGL 1.2.20220720), called in Python, which directly generates NIfTI files from DICOM series. PET data (with file extensions .hdr/.img) were converted to NIfTI using the 'NiBabel' library in Python, either by parsing headers and binary image files with 'NumPy', followed by NIfTI creation, or by reading header-image pairs and exporting them as NIfTI volumes. These workflows were implemented in Python (version 3.13.2).

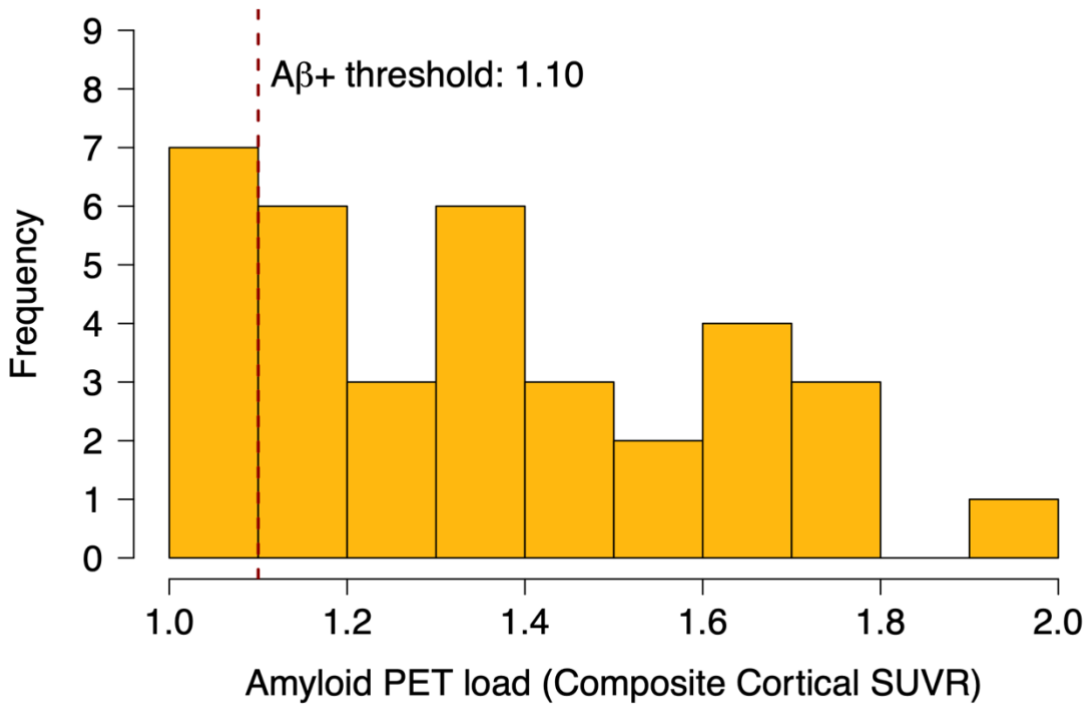
3. Visualization

Associations between CSF synaptic proteins and regional amyloid burden that remained significant after accounting for gray matter volume (FDR-corrected $p_{ADE} < 0.05$) were visualized separately for each protein. Volumes of interest (VOIs) were defined using the Brainnetome atlas (246-region maximum probability map, 25% threshold, 1.25 mm resolution) [2] in Montreal Neurological Institute (MNI) space, with each VOI composed of its corresponding Brainnetome subregions (Supplementary Table S3). Each significant VOI was colored according to the FDR-corrected p-value of its ADE, on a linear color scale ranging from 0 (yellow) to 0.05 (red). Because regional amyloid burden was calculated as the mean across both hemispheres, VOI values were identical for the left and right hemispheres; associations are therefore displayed on the left hemisphere.

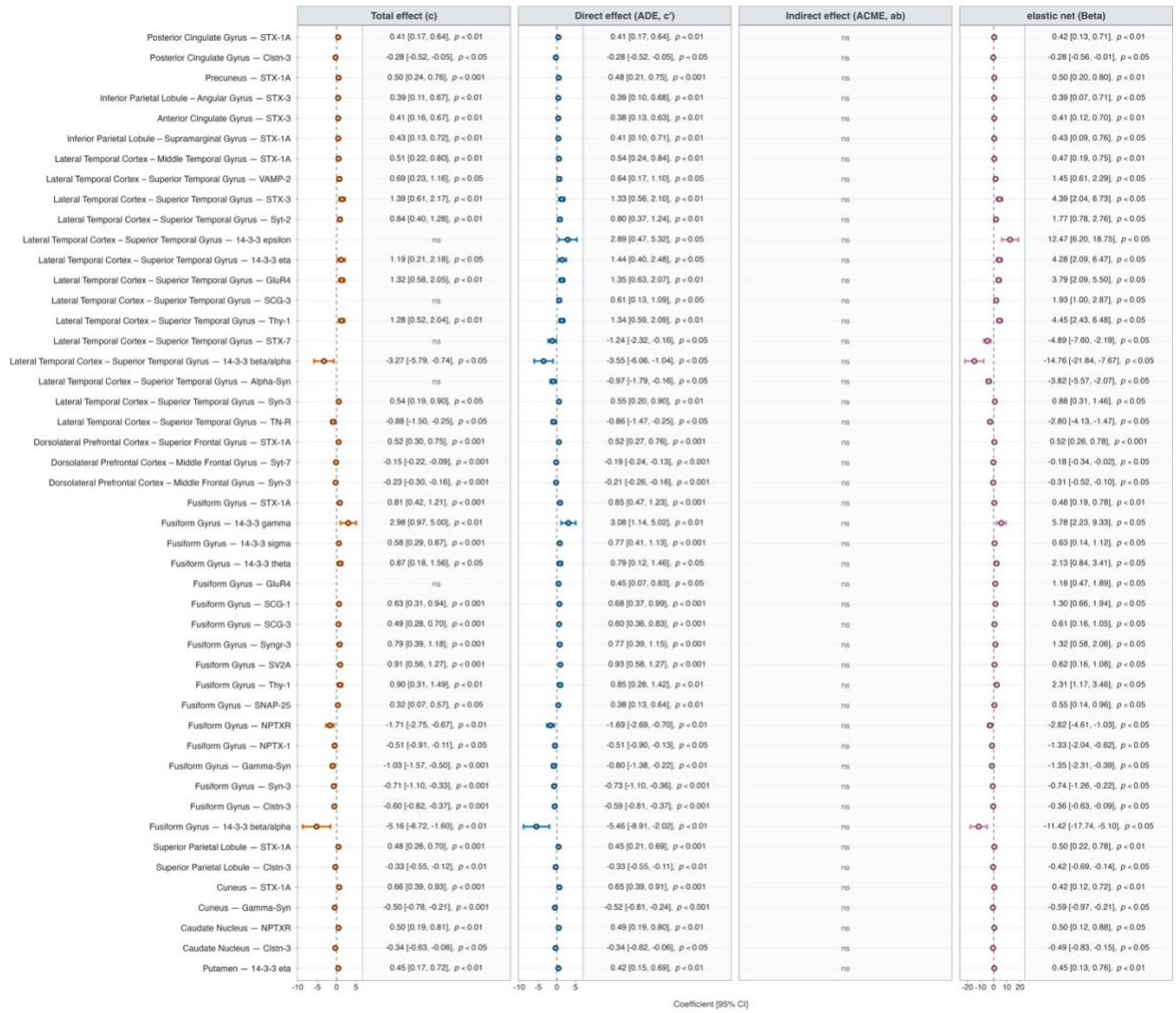
Two complementary visualizations were created. First, for cortical surface views, the volumetric VOIs were projected onto the fsaverage5 pial surface by sampling each VOI mask at 10 depths between the white matter and pial surfaces; each vertex was assigned to the VOI with the highest sampled overlap (minimum 0.3). Results were displayed in lateral and medial views on a surface shaded by sulcal depth. Second, for 3D renderings, the surface of each VOI was reconstructed from its atlas mask using Gaussian smoothing ($\sigma = 1$ voxel), the marching cubes algorithm, and Taubin smoothing. The VOIs were rendered with partial transparency inside a semi-transparent cortical surface shaded by sulcal depth, so that deep VOIs (e.g., caudate nucleus, putamen, and cingulate cortex) remained visible together with cortical VOIs.

Visualizations were generated in Python (version 3.12.3) using 'nibabel' (version 5.4.2) for image handling; 'nilearn' (version 0.14.1) for the MNI152 template, fsaverage5 surfaces, and volume-to-surface projection; 'scikit-image' (version 0.26.0) and 'SciPy' (version 1.17.1) for surface reconstruction and smoothing; 'PyVista' (version 0.49.0; VTK version 9.7.1) for 3D rendering; and 'NumPy' (version 2.4.4), 'pandas' (version 3.0.2), and 'matplotlib' (version 3.10.8) for

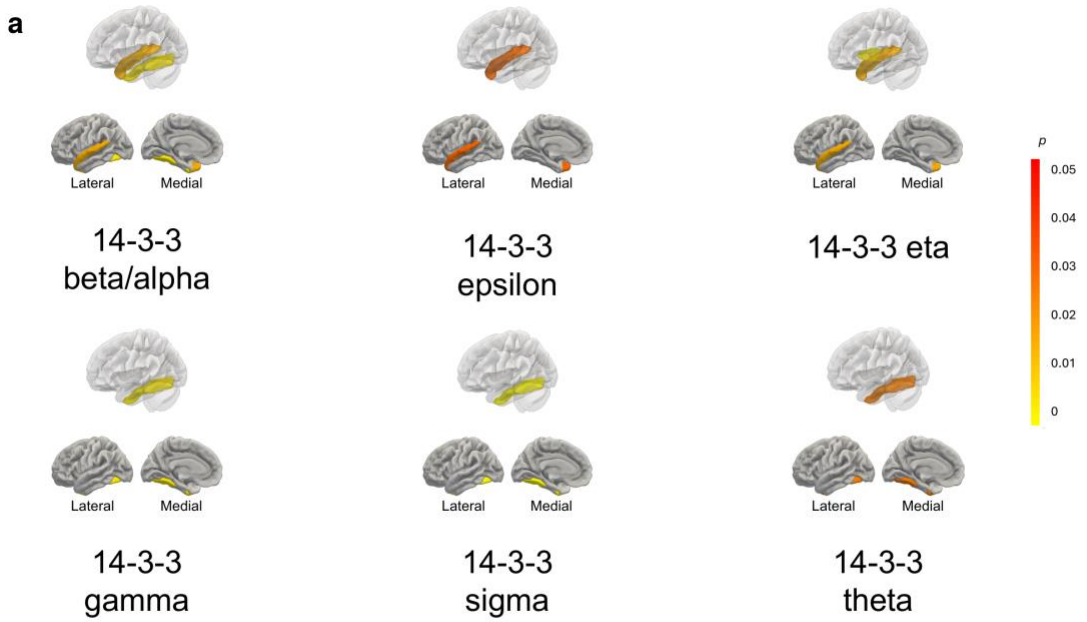
numerical operations, data handling, and color mapping. Scatter plots were created in R ('ggplot2' package) as added-variable (partial regression) plots: regional SUVR and the protein level were each residualized on age, sex, APOE ε4, education, and the other proteins selected by the elastic net in the same region (missing protein values were mean-imputed, as in the main analysis), and re-centred on their observed means, so that the regression line represents the adjusted association; only measured protein values are displayed. A forest plot was created in R ('ggplot2' package) to visualize the coefficients and corresponding 95% confidence intervals from the elastic-net regression and mediation analyses.

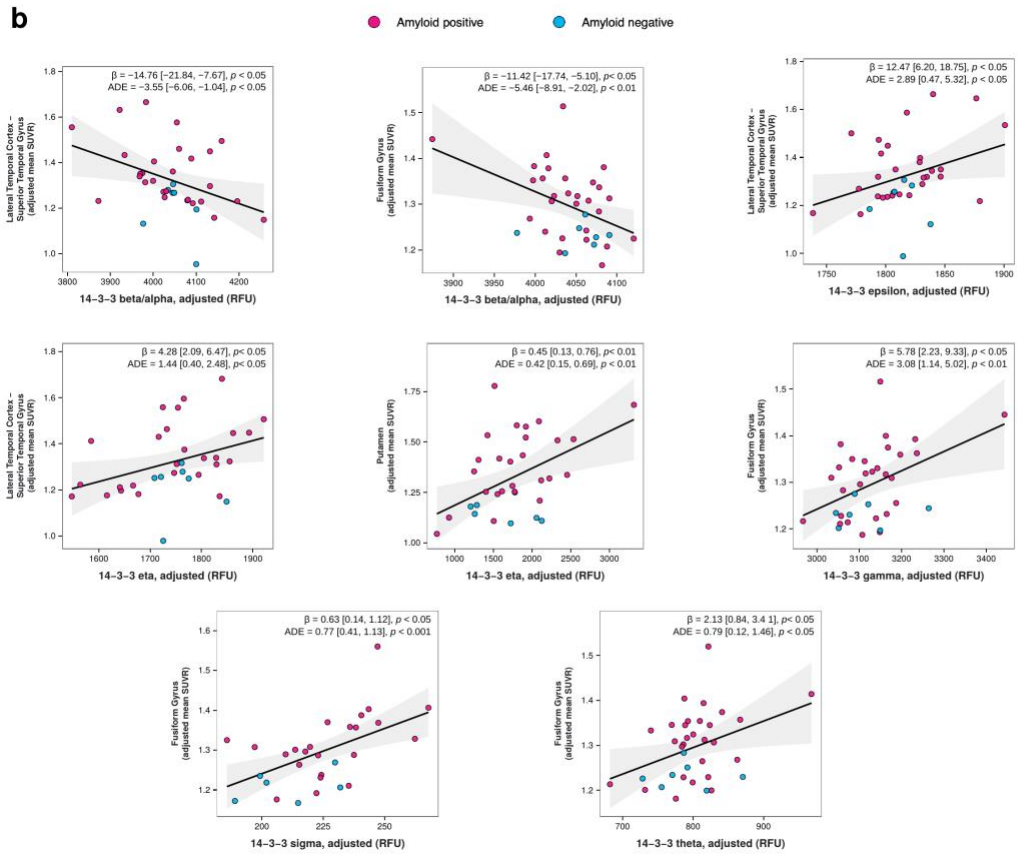


Supplementary Figure S1. Distribution of global cerebral amyloid burden. The histogram plots of amyloid (n = 35) PET standardized uptake value ratios (SUVRs) are visualized. The vertical dashed line represents the threshold of amyloid PET positivity (SUVR ≥ 1.10).

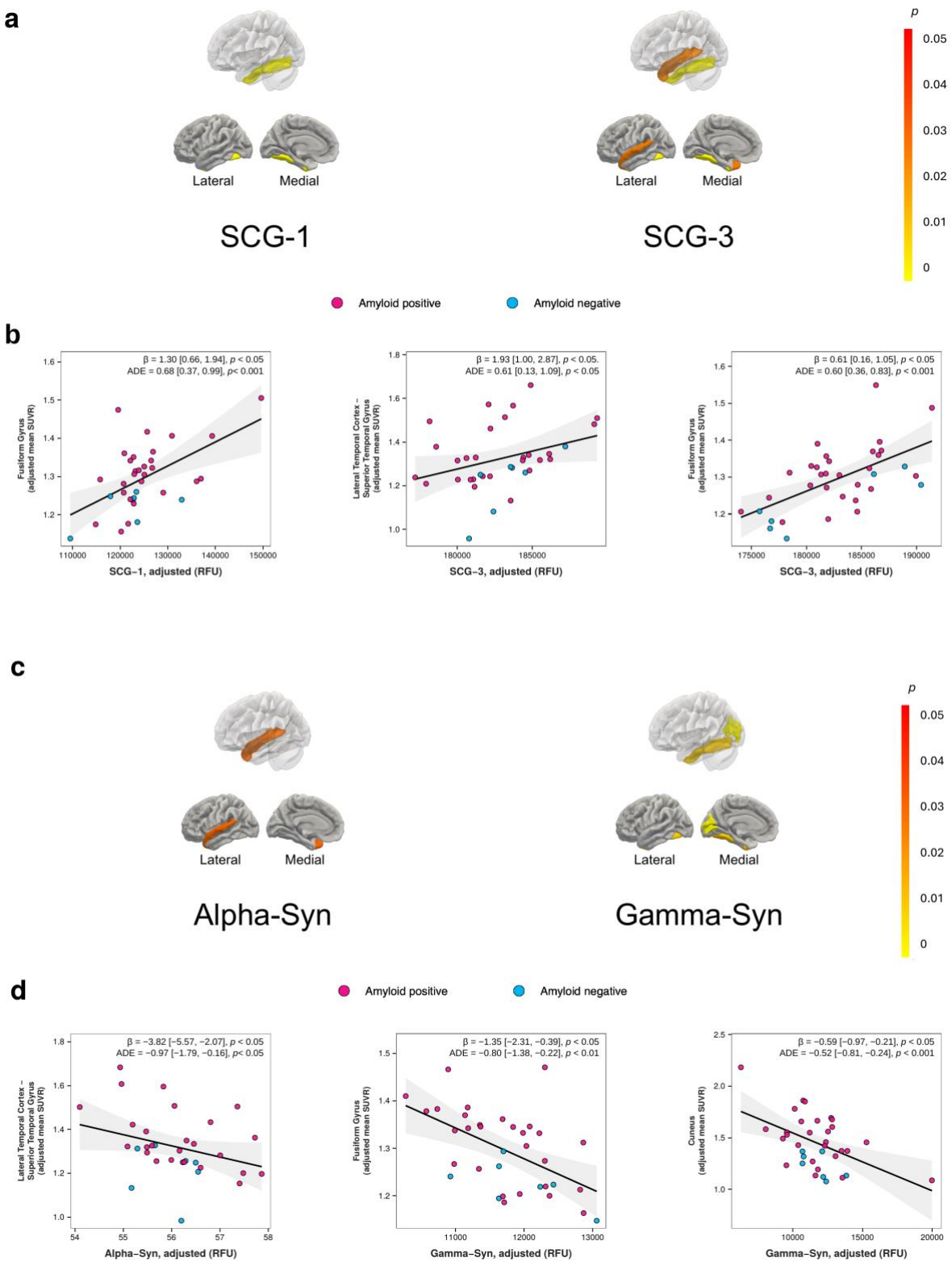


Supplementary Figure S2. Elastic net and mediation estimates of cerebrospinal fluid synaptic protein–amyloid associations. Forest plots show the total effect (c), average direct effect (ADE, c′), average causal mediation effect (ACME, ab) through regional gray matter volume, and elastic net regression coefficient (β) for each protein–region association. Points represent effect estimates, horizontal error bars indicate 95% confidence intervals (CIs), and the dashed vertical line denotes the null value of zero. Positive estimates indicate associations between higher CSF protein levels and greater regional amyloid burden, whereas negative estimates indicate inverse associations. Models were adjusted for age, sex, APOE ε4, and education. Reported p-values were corrected using the Benjamini–Hochberg false discovery rate; ns denotes a non-significant association. No significant indirect effects through gray matter volume were observed.


a
Lateral
Medial
14-3-3 beta/alpha
14-3-3 epsilon
14-3-3 eta
14-3-3 gamma
14-3-3 sigma
14-3-3 theta
p
0.05
0.04
0.03
0.02
0.01
0

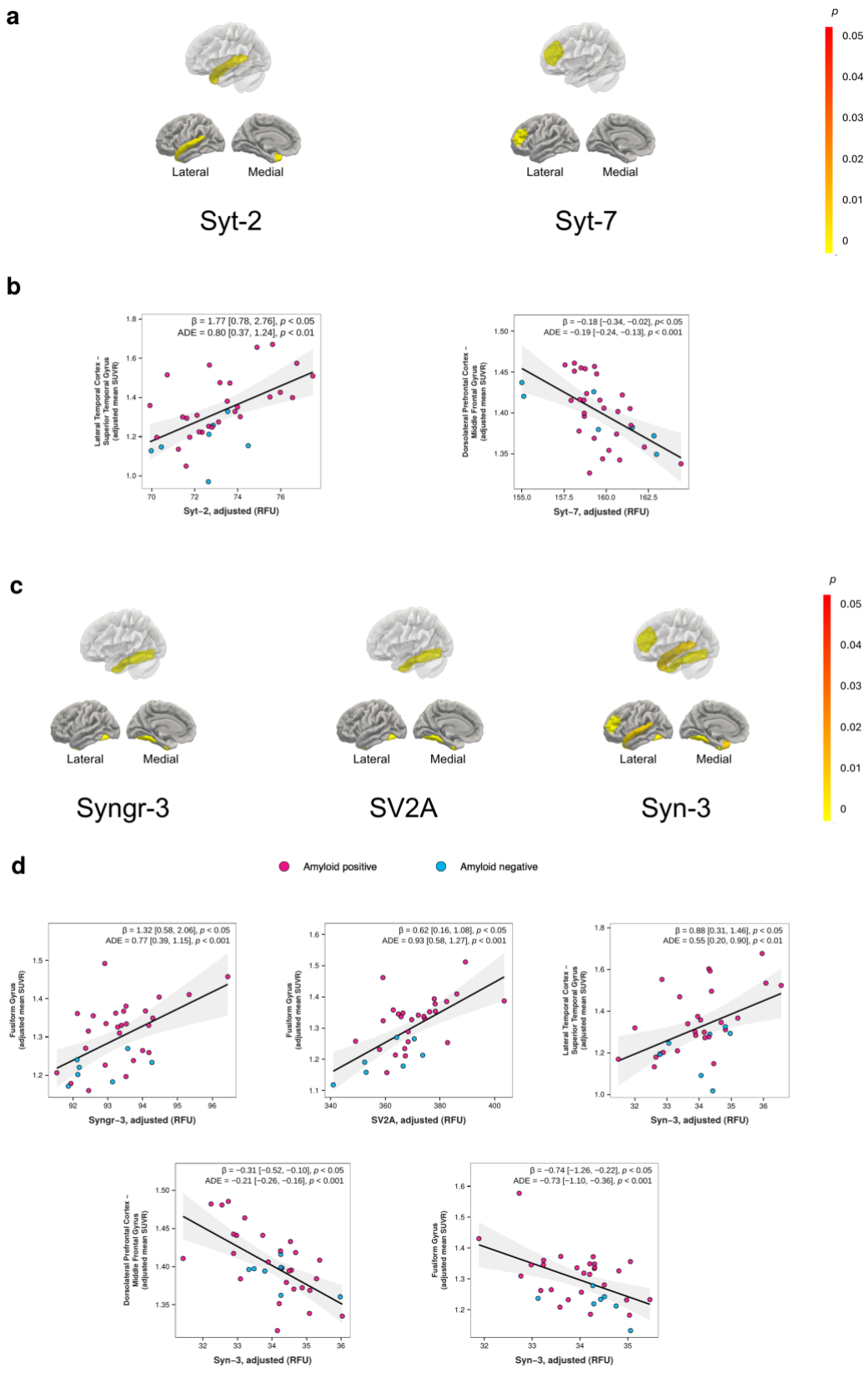

b
Amyloid positive
Amyloid negative
β = −14.76 [−21.84, −7.67], p < 0.05
ADE = −3.55 [−6.06, −1.04], p < 0.05
Lateral Temporal Cortex – Superior Temporal Gyrus (adjusted mean SUVR)
14–3–3 beta/alpha, adjusted (RFU)
β = −11.42 [−17.74, −5.10], p< 0.05
ADE = −5.46 [−8.91, −2.02], p < 0.01
Fusiform Gyrus (adjusted mean SUVR)
14–3–3 beta/alpha, adjusted (RFU)
β = 12.47 [6.20, 18.75], p < 0.05
ADE = 2.89 [0.47, 5.32], p < 0.05
Lateral Temporal Cortex – Superior Temporal Gyrus (adjusted mean SUVR)
14–3–3 epsilon, adjusted (RFU)
β = 4.28 [2.09, 6.47], p< 0.05
ADE = 1.44 [0.40, 2.48], p< 0.05
Lateral Temporal Cortex – Superior Temporal Gyrus (adjusted mean SUVR)
14–3–3 eta, adjusted (RFU)
β = 0.45 [0.13, 0.76], p< 0.01
ADE = 0.42 [0.15, 0.69], p < 0.01
Putamen (adjusted mean SUVR)
14–3–3 eta, adjusted (RFU)
β = 5.78 [2.23, 9.33], p < 0.05
ADE = 3.08 [1.14, 5.02], p < 0.01
Fusiform Gyrus (adjusted mean SUVR)
14–3–3 gamma, adjusted (RFU)
β = 0.63 [0.14, 1.12], p < 0.05
ADE = 0.77 [0.41, 1.13], p < 0.001
Fusiform Gyrus (adjusted mean SUVR)
14–3–3 sigma, adjusted (RFU)
β = 2.13 [0.84, 3.4 1], p< 0.05
ADE = 0.79 [0.12, 1.46], p < 0.05
Fusiform Gyrus (adjusted mean SUVR)
14–3–3 theta, adjusted (RFU)

Supplementary Figure S3. Regional amyloid associations with the 14-3-3 proteins 14-3-3 protein beta/alpha, epsilon, eta, gamma, sigma, and theta. **a** Regional associations for each protein, shown on the left hemisphere as a 3D rendering (top) and on the lateral and medial cortical surfaces (bottom); regional values are bilateral means. The color bar indicates Benjamini–Hochberg false discovery rate (FDR)-corrected p-values. **b** Scatter plots showing the associations of cerebrospinal fluid (CSF) 14-3-3 protein levels with regional amyloid burden. CSF protein levels (relative fluorescence units, RFU) and regional amyloid burden (mean standardized uptake value ratio, SUVR) are shown adjusted for age, sex, APOE ε4, education, and the other proteins selected in the same region (added-variable plots); the regression line therefore reflects the adjusted association. The gray shaded area represents the 95% confidence interval around the regression line. Blue dots: amyloid-negative; red dots: amyloid-positive cases.



Supplementary Figure S4. Regional amyloid associations with the secretogranins secretogranin-1 (SCG-1) and secretogranin-3 (SCG-3) and the synucleins α-synuclein (α-Syn) and γ-synuclein (γ-Syn). **a** Regional associations for SCG-1 and SCG-3, shown on the left

hemisphere as a 3D rendering (top) and on the lateral and medial cortical surfaces (bottom); regional values are bilateral means. The color bars indicate Benjamini–Hochberg false discovery rate (FDR)-corrected p-values. **b** Scatter plots showing the associations of cerebrospinal fluid (CSF) SCG-1 and SCG-3 levels with regional amyloid burden. **c** Regional associations for α-Syn and γ-Syn, shown as in **a**. **d** Scatter plots showing the associations of CSF α-Syn and γ-Syn levels with regional amyloid burden. CSF protein levels (relative fluorescence units, RFU) and regional amyloid burden (mean standardized uptake value ratio, SUVR) are shown adjusted for age, sex, APOE ε4, education, and the other proteins selected in the same region (added-variable plots); the regression lines therefore reflect the adjusted associations. The gray shaded areas represent the 95% confidence intervals around the regression lines. Blue dots: amyloid-negative; red dots: amyloid-positive cases.



Supplementary Figure S5. Regional amyloid associations with the synaptotagmins synaptotagmin-2 (Syt-2) and synaptotagmin-7 (Syt-7) and the vesicle pool regulation and

trafficking proteins synaptogyrin-3 (Syngr-3), synaptic vesicle glycoprotein 2A (SV2A), and synapsin-3 (Syn-3). **a** Regional associations for Syt-2 and Syt-7, shown on the left hemisphere as a 3D rendering (top) and on the lateral and medial cortical surfaces (bottom); regional values are bilateral means. The color bars indicate Benjamini–Hochberg false discovery rate (FDR)-corrected p-values. **b** Scatter plots showing the associations of cerebrospinal fluid (CSF) Syt-2 and Syt-7 levels with regional amyloid burden. **c** Regional associations for Syngr-3, SV2A, and Syn-3, shown as in **a**. **d** Scatter plots showing the associations of CSF Syngr-3, SV2A, and Syn-3 levels with regional amyloid burden. CSF protein levels (relative fluorescence units, RFU) and regional amyloid burden (mean standardized uptake value ratio, SUVR) are shown adjusted for age, sex, APOE ε4, education, and the other proteins selected in the same region (added-variable plots); the regression lines therefore reflect the adjusted associations. The gray shaded areas represent the 95% confidence intervals around the regression lines. Blue dots: amyloid-negative; red dots: amyloid-positive cases.

References

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Supplementary Tables

Supplementary Table S1. The list of synaptic proteins included in this study.

Protein
14-3-3 protein beta/alpha
14-3-3 protein epsilon
14-3-3 protein eta
14-3-3 protein gamma
14-3-3 protein sigma
14-3-3 protein theta
14-3-3 protein zeta/delta
Alpha-synuclein
Calsyntenin-3
Gamma-synuclein
Glutamate receptor 4
Neuregulin-1
Neuregulin-1, sensory and motor neuron-derived factor isoform
Neurogranin
Neuronal pentraxin receptor
Neuronal pentraxin-1
Neuronal pentraxin-2
Pro-neuregulin-3, membrane-bound isoform
Secretogranin-1
Secretogranin-3
Synapsin-3
Synaptic vesicle glycoprotein 2A
Synaptogyrin-3
Synaptosomal-associated protein 25
Synaptotagmin-1
Synaptotagmin-2
Synaptotagmin-7
Syntaxin-1A
Syntaxin-1B
Syntaxin-3
Syntaxin-7
Tenascin-R
Thy-1 membrane glycoprotein
Vesicle-associated membrane protein 2
Visinin-like protein 1

Supplementary Table S2. ADNI-based list of the 35 mild cognitive impairment (MCI) cases included in this study.

Subject codes are ADNI ID codes.

Subject
sub_011_S_2274
sub_013_S_2324
sub_013_S_2389
sub_014_S_2308
sub_018_S_2133
sub_018_S_2155
sub_022_S_2087
sub_022_S_2167
sub_022_S_2379
sub_032_S_2247
sub_035_S_2061
sub_035_S_2074
sub_035_S_2199
sub_036_S_2380
sub_053_S_2396
sub_057_S_2398
sub_067_S_2195
sub_067_S_2196
sub_068_S_2168
sub_068_S_2171
sub_068_S_2187
sub_068_S_2193
sub_068_S_2248
sub_068_S_2316
sub_073_S_2153
sub_073_S_2190
sub_073_S_2225
sub_128_S_2045
sub_128_S_2130
sub_128_S_2151
sub_128_S_2220
sub_130_S_2373
sub_130_S_2391
sub_141_S_2333
sub_941_S_2060

Supplementary Table S3. Volumes of interest (VOI) and their corresponding region category. Region categories were assigned based on previous studies of regional amyloid deposition.[3–10]

Region	Region category
Precuneus	Core DMN hub
Posterior cingulate gyrus	Core DMN hub
Medial orbitofrontal cortex	Core DMN hub / frontomedial cortex
Lateral Inferior parietal lobule – angular gyrus	DMN-associated lateral parietal region
Anterior cingulate gyrus	DMN-associated Cingulate association cortex
Lateral temporal cortex – middle temporal gyrus	Extended DMN-related temporal association cortex
Lateral temporal cortex – superior temporal gyrus	Extended DMN-related temporal association cortex
Lateral Inferior parietal lobule – supramarginal gyrus	Temporoparietal association cortex
Dorsolateral prefrontal cortex – superior frontal gyrus	Prefrontal association cortex
Dorsolateral prefrontal cortex – middle frontal gyrus	Prefrontal association cortex
Fusiform gyrus	Temporobasal association cortex
Superior parietal lobule	Parietal association cortex
Cuneus	Occipital cortex
Lingual gyrus	Occipital cortex
Occipital pole	Occipital cortex
Caudate nucleus	Striatum
Putamen	Striatum

Supplementary Table S4. Mean standardized uptake value ratio (SUVR) for amyloid burden per volume of interest (VOI).

SUVR values with corresponding Brainnetome parcel ID, and labels are shown for each volume of interest (VOI).

Regions	SUVR	Brainnetome parcel ID	Brainnetome labels
Precuneus	1.38 ± 0.30	BN142, BN145	A7m, A31, dmPOS (PEr)
Posterior Cingulate Gyrus	1.51 ± 0.39	BN175	A23d, A23v
Medial Orbitofrontal Cortex	1.48 ± 0.33	BN41, BN42	A11m, A14m
Inferior Parietal Lobule – Angular Gyrus	1.37 ± 0.36	BN138	A39c, A39rd, A39rv
Anterior Cingulate Gyrus	1.45 ± 0.34	BN178, BN179, BN180, BN187, BN188	A24rv, A32p
Lateral Temporal Cortex – Middle Temporal Gyrus	1.37 ± 0.30	BN81, BN82, BN85, BN86, BN87, BN88, BN121, BN122, BN123	A21c, A21r
Lateral Temporal Cortex – Superior Temporal Gyrus	1.32 ± 0.27	BN71, BN72, BN73, BN76, BN80, BN124	A22c, A22r
Inferior Parietal Lobule – Supramarginal Gyrus	1.40 ± 0.28	BN146	A40c, A40rd, A40rv
Dorsolateral Prefrontal Cortex – Superior Frontal Gyrus	1.36 ± 0.32	BN3, BN4, BN5, BN6, BN7, BN8, BN11, BN13, BN14, BN19, BN20, BN28	A9m, A8m
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	1.40 ± 0.34	BN16, BN21, BN22, BN23, BN24, BN26	A9/46d, A9/46v
Fusiform Gyrus	1.30 ± 0.19	BN104, BN105, BN106, BN109	A20rv, A37mv, A37lv
Superior Parietal Lobule	1.33 ± 0.24	BN103, BN108	A7pc, A7ip
Cuneus	1.45 ± 0.34	BN147, BN148, BN149, BN150, BN151, BN152, BN153, BN154	rCunG, cCunG
Lingual Gyrus	1.25 ± 0.15	BN189, BN190, BN195, BN196	cLinG, rLinG
Occipital Pole	1.23 ± 0.19	BN199, BN203, BN204	OPC
Caudate Nucleus	1.14 ± 0.24	BN219, BN227, BN228	Ventral and dorsal caudate parcels
Putamen	1.32 ± 0.22	BN59, BN66, BN67	Ventromedial and dorsolateral putamen parcels

Supplementary Table S5. Mean gray matter volume for each volume of interest (VOI), normalized to total intracranial volume (TIV).

Regions	GM Volumes
Precuneus	9.50 ± 0.36
Posterior Cingulate Gyrus	3.44 ± 0.34
Medial Orbitofrontal Cortex	5.16 ± 0.60
Inferior Parietal Lobule – Angular Gyrus	12.68 ± 1.54
Anterior Cingulate Gyrus	2.61 ± 0.44
Lateral Temporal Cortex – Middle Temporal Gyrus	6.23 ± 0.66
Lateral Temporal Cortex – Superior Temporal Gyrus	4.25 ± 0.49
Inferior Parietal Lobule – Supramarginal Gyrus	11.92 ± 1.25
Dorsolateral Prefrontal Cortex – Superior Frontal Gyrus	5.88 ± 0.77
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	6.63 ± 1.03
Fusiform Gyrus	13.36 ± 1.13
Superior Parietal Lobule	2.42 ± 0.32
Cuneus	5.8 ± 0.80
Lingual Gyrus	6.35 ± 0.61
Occipital Pole	3.96 ± 0.49
Caudate Nucleus	3.07 ± 1.19
Putamen	3.10 ± 0.32

Supplementary Table S6. Significant associations between CSF synaptic protein levels and regional amyloid burden.

Results were based on elastic net models adjusted for age, sex, APOE ε4, and education. For each protein–region association, the table reports the elastic net regression coefficient (β), 95% confidence interval (CI), and uncorrected and Benjamini–Hochberg false discovery rate (BH-FDR)-corrected p-values.

Positive β coefficients indicate associations between higher CSF protein levels and greater regional amyloid burden, whereas negative coefficients indicate inverse associations. Only associations with BH-FDR-corrected $p < 0.05$ are reported.

Region	Protein	Elastic net Beta	95% CI (lower)	95% CI (upper)	p (uncorrected)	p(FDR-BH corrected)
Anterior Cingulate Gyrus	Syntaxin-3	0.411	0.120	0.703	0.007	0.007
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Syntaxin-1A	0.496	0.220	0.771	9.48e-04	9.48e-04
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Secretogranin-1	0.467	0.157	0.778	0.005	0.040
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	14-3-3 protein beta/alpha	−2.339	−2.760	−1.918	3.94e-04	0.005
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	14-3-3 protein eta	2.355	1.570	3.140	0.002	0.007
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	14-3-3 protein sigma	0.630	0.415	0.845	0.003	0.007
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	14-3-3 protein theta	1.637	1.184	2.090	0.001	0.007
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Calsyntenin-3	−1.206	−1.476	−0.935	7.58e-04	0.005
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Glutamate receptor 4	0.607	0.278	0.936	0.010	0.016
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Neuregulin-1	−0.795	−1.069	−0.522	0.003	0.007
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Neuregulin-1, sensory and motor neuron-derived factor isoform	0.453	0.206	0.701	0.010	0.016
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Neuronal pentraxin-1	−0.455	−0.744	−0.165	0.015	0.021
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Neuronal pentraxin-2	1.584	0.959	2.210	0.004	0.009
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Pro-neuregulin-3, membrane-bound isoform	−3.142	−3.851	−2.433	7.71e-04	0.005
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Secretogranin-3	−0.543	−0.846	−0.240	0.011	0.016
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Synapsin-3	−0.309	−0.522	−0.096	0.019	0.024
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Synaptic vesicle glycoprotein 2A	0.434	0.092	0.776	0.027	0.033
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Synaptogyrin-3	0.285	0.124	0.446	0.011	0.016
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Synaptosomal-associated protein 25	−0.167	−0.303	−0.031	0.030	0.035
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Synaptotagmin-1	−1.840	−2.795	−0.885	0.009	0.016
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Synaptotagmin-2	0.395	0.215	0.575	0.006	0.012
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Synaptotagmin-7	−0.178	−0.340	−0.016	0.039	0.044
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Syntaxin-7	1.292	0.841	1.743	0.003	0.007
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Tenascin-R	−0.979	−1.281	−0.678	0.002	0.007
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Thy-1 membrane glycoprotein	1.332	1.087	1.576	4.18e-04	0.005
Dorsolateral Prefrontal Cortex – Superior Frontal Gyrus	Syntaxin-1A	0.521	0.263	0.780	2.86e-04	2.86e-04
Fusiform Gyrus	Calsyntenin-3	−0.358	−0.629	−0.086	0.012	0.036
Fusiform Gyrus	Syntaxin-1A	0.482	0.189	0.776	0.002	0.002
Fusiform Gyrus	14-3-3 protein beta/alpha	−11.419	−17.742	−5.096	0.007	0.024
Fusiform Gyrus	14-3-3 protein epsilon	5.284	1.984	8.584	0.011	0.024
Fusiform Gyrus	14-3-3 protein gamma	5.777	2.227	9.327	0.011	0.024
Fusiform Gyrus	14-3-3 protein theta	2.127	0.845	3.409	0.010	0.024
Fusiform Gyrus	Glutamate receptor 4	1.180	0.466	1.894	0.010	0.024
Fusiform Gyrus	Neuronal pentraxin receptor	−2.822	−4.611	−1.034	0.012	0.024

Region	Protein	Elastic net Beta	95% CI (lower)	95% CI (upper)	p (uncorrected)	p(FDR-BH corrected)
Fusiform Gyrus	Neuronal pentraxin-1	−1.330	−2.037	−0.623	0.006	0.024
Fusiform Gyrus	Secretogranin-1	1.296	0.656	1.936	0.005	0.024
Fusiform Gyrus	Secretogranin-3	0.607	0.160	1.054	0.020	0.036
Fusiform Gyrus	Synaptogyrin-3	1.316	0.577	2.055	0.008	0.024
Fusiform Gyrus	Synaptotagmin-2	1.131	0.482	1.780	0.008	0.024
Fusiform Gyrus	Thy-1 membrane glycoprotein	2.314	1.167	3.462	0.005	0.024
Fusiform Gyrus	Vesicle-associated membrane protein 2	1.009	0.462	1.557	0.007	0.024
Fusiform Gyrus	14-3-3 protein sigma	0.634	0.144	1.125	0.026	0.039
Fusiform Gyrus	Gamma-synuclein	−1.346	−2.307	−0.386	0.021	0.035
Fusiform Gyrus	Synapsin-3	−0.740	−1.255	−0.225	0.020	0.035
Fusiform Gyrus	Synaptosomal-associated protein 25	0.553	0.142	0.964	0.023	0.037
Fusiform Gyrus	Synaptic vesicle glycoprotein 2A	0.616	0.157	1.075	0.029	0.047
Inferior Parietal Lobule – Supramarginal Gyrus	Syntaxin-1A	0.426	0.089	0.763	0.015	0.015
Inferior Parietal Lobule – Angular Gyrus	Syntaxin-3	0.390	0.070	0.710	0.019	0.019
Lateral Temporal Cortex – Middle Temporal Gyrus	Syntaxin-1A	0.467	0.186	0.748	0.002	0.002
Lateral Temporal Cortex – Middle Temporal Gyrus	Calsyntenin-3	−1.242	−2.004	−0.479	0.009	0.043
Lateral Temporal Cortex – Middle Temporal Gyrus	Glutamate receptor 4	1.355	0.533	2.177	0.008	0.043
Lateral Temporal Cortex – Middle Temporal Gyrus	Pro-neuregulin-3, membrane-bound isoform	−3.227	−5.060	−1.395	0.006	0.043
Lateral Temporal Cortex – Middle Temporal Gyrus	Synaptotagmin-2	1.039	0.403	1.674	0.008	0.043
Lateral Temporal Cortex – Middle Temporal Gyrus	Thy-1 membrane glycoprotein	1.500	0.718	2.282	0.004	0.043
Lateral Temporal Cortex – Superior Temporal Gyrus	Syntaxin-1A	0.440	0.133	0.747	0.007	0.007
Lateral Temporal Cortex – Superior Temporal Gyrus	14-3-3 protein beta/alpha	−14.758	−21.844	−7.671	0.012	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	14-3-3 protein epsilon	12.475	6.197	18.753	0.013	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	14-3-3 protein eta	4.282	2.091	6.472	0.014	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Alpha-synuclein	−3.817	−5.567	−2.066	0.011	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Glutamate receptor 4	3.795	2.093	5.496	0.011	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Neuronal pentraxin receptor	−7.752	−11.661	−3.843	0.013	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Neuronal pentraxin-2	3.338	1.550	5.127	0.015	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Pro-neuregulin-3, membrane-bound isoform	−1.697	−2.927	−0.468	0.027	0.045
Lateral Temporal Cortex – Superior Temporal Gyrus	Secretogranin-3	1.934	1.002	2.866	0.012	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Synapsin-3	0.882	0.307	1.458	0.022	0.039
Lateral Temporal Cortex – Superior Temporal Gyrus	Synaptotagmin-2	1.771	0.777	2.764	0.017	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Synaptotagmin-7	−1.021	−1.689	−0.352	0.022	0.039
Lateral Temporal Cortex – Superior Temporal Gyrus	Syntaxin-3	4.388	2.043	6.733	0.015	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Syntaxin-7	−4.895	−7.601	−2.189	0.016	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Tenascin-R	−2.802	−4.133	−1.471	0.012	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Thy-1 membrane glycoprotein	4.454	2.428	6.480	0.011	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Vesicle-associated membrane protein 2	1.451	0.609	2.293	0.018	0.035
Medial Orbitofrontal Cortex	Syntaxin-1A	0.538	0.276	0.800	2.30e-04	2.30e-04
Medial Orbitofrontal Cortex	Calsyntenin-3	−0.281	−0.525	−0.038	0.025	0.025
Medial Orbitofrontal Cortex	14-3-3 protein beta/alpha	−10.545	−12.177	−8.912	0.001	0.004
Medial Orbitofrontal Cortex	14-3-3 protein epsilon	8.684	7.235	10.133	0.002	0.004

Region	Protein	Elastic net Beta	95% CI (lower)	95% CI (upper)	p (uncorrected)	p(FDR-BH corrected)
Medial Orbitofrontal Cortex	14-3-3 protein eta	3.527	3.009	4.044	0.001	0.004
Medial Orbitofrontal Cortex	14-3-3 protein sigma	0.838	0.677	0.999	0.002	0.004
Medial Orbitofrontal Cortex	Alpha-synuclein	−2.815	−3.219	−2.412	0.001	0.004
Medial Orbitofrontal Cortex	Gamma-synuclein	1.605	1.206	2.004	0.003	0.005
Medial Orbitofrontal Cortex	Glutamate receptor 4	3.176	2.782	3.571	8.33e-04	0.004
Medial Orbitofrontal Cortex	Neuregulin-1	−0.391	−0.564	−0.218	0.010	0.012
Medial Orbitofrontal Cortex	Neuronal pentraxin receptor	−6.145	−7.062	−5.228	0.001	0.004
Medial Orbitofrontal Cortex	Neuronal pentraxin-1	−0.821	−1.067	−0.575	0.005	0.007
Medial Orbitofrontal Cortex	Neuronal pentraxin-2	2.742	2.309	3.175	0.001	0.004
Medial Orbitofrontal Cortex	Pro-neuregulin-3, membrane-bound isoform	−1.602	−1.887	−1.317	0.002	0.004
Medial Orbitofrontal Cortex	Secretogranin-1	0.234	0.046	0.422	0.033	0.034
Medial Orbitofrontal Cortex	Secretogranin-3	1.813	1.580	2.047	8.92e-04	0.004
Medial Orbitofrontal Cortex	Synapsin-3	0.387	0.248	0.526	0.007	0.009
Medial Orbitofrontal Cortex	Synaptic vesicle glycoprotein 2A	−0.233	−0.420	−0.046	0.033	0.034
Medial Orbitofrontal Cortex	Synaptogyrin-3	0.261	0.147	0.375	0.010	0.012
Medial Orbitofrontal Cortex	Synaptotagmin-2	1.322	1.087	1.557	0.002	0.004
Medial Orbitofrontal Cortex	Synaptotagmin-7	−0.655	−0.811	−0.498	0.003	0.005
Medial Orbitofrontal Cortex	Syntaxin-1B	−0.155	−0.273	−0.037	0.030	0.033
Medial Orbitofrontal Cortex	Syntaxin-3	3.079	2.517	3.642	0.002	0.004
Medial Orbitofrontal Cortex	Syntaxin-7	−3.127	−3.765	−2.488	0.002	0.004
Medial Orbitofrontal Cortex	Tenascin-R	−2.002	−2.372	−1.633	0.002	0.004
Medial Orbitofrontal Cortex	Thy-1 membrane glycoprotein	3.477	3.010	3.945	9.75e-04	0.004
Medial Orbitofrontal Cortex	Vesicle-associated membrane protein 2	0.653	0.441	0.865	0.006	0.008
Cuneus	Syntaxin-1A	0.418	0.116	0.720	0.008	0.008
Cuneus	Gamma-synuclein	−0.589	−0.970	−0.207	0.004	0.038
Lingual Gyrus	Calsyntenin-3	−0.453	−0.735	−0.171	0.003	0.008
Lingual Gyrus	Syntaxin-1A	0.347	0.071	0.623	0.016	0.016
Lingual Gyrus	14-3-3 protein beta/alpha	−0.726	−1.315	−0.137	0.018	0.045
Lingual Gyrus	Synaptic vesicle glycoprotein 2A	0.535	0.095	0.975	0.019	0.045
Lingual Gyrus	14-3-3 protein zeta/delta	−0.487	−0.855	−0.119	0.012	0.035
Lingual Gyrus	14-3-3 protein epsilon	67.382	43.113	91.651	0.018	0.024
Lingual Gyrus	14-3-3 protein gamma	40.607	25.803	55.412	0.018	0.024
Lingual Gyrus	14-3-3 protein theta	−10.344	−14.434	−6.253	0.020	0.024
Lingual Gyrus	Alpha-synuclein	−17.969	−24.365	−11.574	0.018	0.024
Lingual Gyrus	Gamma-synuclein	−7.389	−9.914	−4.863	0.017	0.024
Lingual Gyrus	Glutamate receptor 4	13.224	8.777	17.672	0.017	0.024
Lingual Gyrus	Neuregulin-1	9.045	5.733	12.357	0.018	0.024
Lingual Gyrus	Neuregulin-1, sensory and motor neuron-derived factor isoform	−7.337	−9.893	−4.782	0.017	0.024
Lingual Gyrus	Neuronal pentraxin receptor	−54.218	−73.532	−34.903	0.018	0.024
Lingual Gyrus	Neuronal pentraxin-1	−13.074	−17.586	−8.562	0.017	0.024
Lingual Gyrus	Neuronal pentraxin-2	3.504	2.383	4.625	0.016	0.024

Region	Protein	Elastic net Beta	95% CI (lower)	95% CI (upper)	p (uncorrected)	p(FDR-BH corrected)
Lingual Gyrus	Pro-neuregulin-3, membrane-bound isoform	36.687	22.928	50.447	0.019	0.024
Lingual Gyrus	Secretogranin-1	13.636	8.946	18.325	0.017	0.024
Lingual Gyrus	Secretogranin-3	19.470	12.459	26.481	0.018	0.024
Lingual Gyrus	Synaptogyrin-3	8.388	5.493	11.284	0.017	0.024
Lingual Gyrus	Synaptosomal-associated protein 25	3.958	2.550	5.366	0.018	0.024
Lingual Gyrus	Synaptotagmin-1	12.463	7.922	17.005	0.018	0.024
Lingual Gyrus	Syntaxin-1B	3.828	2.385	5.271	0.019	0.024
Lingual Gyrus	Syntaxin-7	−30.904	−42.062	−19.747	0.018	0.024
Lingual Gyrus	Tenascin-R	8.080	5.010	11.150	0.019	0.024
Lingual Gyrus	Thy-1 membrane glycoprotein	12.516	8.256	16.776	0.017	0.024
Lingual Gyrus	Vesicle-associated membrane protein 2	5.184	3.526	6.842	0.016	0.024
Occipital Pole	14-3-3 protein beta/alpha	−10.916	−13.650	−8.181	0.013	0.026
Occipital Pole	14-3-3 protein epsilon	6.383	4.690	8.076	0.013	0.026
Occipital Pole	14-3-3 protein gamma	3.084	0.985	5.182	0.034	0.043
Occipital Pole	14-3-3 protein sigma	−1.515	−1.843	−1.186	0.011	0.026
Occipital Pole	Alpha-synuclein	−2.389	−2.913	−1.865	0.011	0.026
Occipital Pole	Gamma-synuclein	−4.765	−5.597	−3.934	0.009	0.026
Occipital Pole	Neuregulin-1	1.068	0.686	1.450	0.018	0.029
Occipital Pole	Neuregulin-1, sensory and motor neuron-derived factor isoform	−1.873	−2.179	−1.568	0.008	0.026
Occipital Pole	Neurogranin	6.355	4.653	8.056	0.013	0.026
Occipital Pole	Neuronal pentraxin receptor	−7.187	−8.569	−5.806	0.010	0.026
Occipital Pole	Neuronal pentraxin-1	−2.627	−3.264	−1.990	0.012	0.026
Occipital Pole	Pro-neuregulin-3, membrane-bound isoform	4.490	3.520	5.460	0.011	0.026
Occipital Pole	Secretogranin-1	3.070	2.447	3.692	0.010	0.026
Occipital Pole	Secretogranin-3	2.774	2.333	3.214	0.008	0.026
Occipital Pole	Synapsin-3	−0.706	−1.042	−0.370	0.024	0.031
Occipital Pole	Synaptic vesicle glycoprotein 2A	1.145	0.878	1.411	0.012	0.026
Occipital Pole	Synaptogyrin-3	1.766	1.390	2.143	0.011	0.026
Occipital Pole	Synaptotagmin-2	−0.705	−0.983	−0.427	0.020	0.029
Occipital Pole	Syntaxin-1B	0.652	0.382	0.922	0.021	0.029
Occipital Pole	Syntaxin-7	−1.360	−1.830	−0.889	0.017	0.029
Occipital Pole	Tenascin-R	1.830	1.147	2.513	0.019	0.029
Occipital Pole	Vesicle-associated membrane protein 2	−0.452	−0.634	−0.270	0.020	0.029
Occipital Pole	Visinin-like protein 1	2.455	2.048	2.862	0.008	0.026
Occipital Pole	14-3-3 protein eta	−2.707	−3.274	−2.141	0.010	0.030
Occipital Pole	14-3-3 protein theta	3.915	3.130	4.701	0.010	0.030
Occipital Pole	Calsyntenin-3	−1.738	−1.975	−1.502	0.007	0.030
Occipital Pole	Glutamate receptor 4	−0.514	−0.782	−0.247	0.026	0.039
Occipital Pole	Neuronal pentraxin-2	−1.852	−2.596	−1.108	0.020	0.032
Occipital Pole	Synaptotagmin-7	0.220	0.049	0.391	0.039	0.049
Precuneus	Syntaxin-1A	0.499	0.201	0.796	0.002	0.002

Region	Protein	Elastic net Beta	95% CI (lower)	95% CI (upper)	p (uncorrected)	p(FDR-BH corrected)
Caudate Nucleus	Calsyntenin-3	−0.490	−0.827	−0.154	0.006	0.030
Caudate Nucleus	Neuronal pentraxin receptor	0.497	0.116	0.879	0.012	0.012
Putamen	14-3-3 protein eta	0.446	0.134	0.758	0.007	0.007
Superior Parietal Lobule	Calsyntenin-3	−0.416	−0.689	−0.143	0.004	0.027
Superior Parietal Lobule	Syntaxin-1A	0.499	0.219	0.778	0.001	0.001
Posterior Cingulate Gyrus	Syntaxin-1A	0.424	0.134	0.713	0.006	0.006
Posterior Cingulate Gyrus	Calsyntenin-3	−0.284	−0.558	−0.010	0.043	0.043

Supplementary Table S7. Regional CSF synaptic protein-amyloid associations independent of gray matter volume.

For each protein–region association identified by the elastic net models, elastic net regression coefficient (β), 95% confidence interval (CI), and uncorrected and Benjamini–Hochberg false discovery rate (BH-FDR)-corrected p-values.

Mediation results include the average causal mediation effect (ACME), average direct effect (ADE), and total effect, together with their standard errors (SEs), 95% CIs, and corresponding uncorrected and BH-FDR-corrected p-values.

Models were adjusted for age, sex, APOE ε4, and education, with regional gray matter volume included as the mediator. Statistical significance was defined as a BH-FDR-corrected $p < 0.05$.

Region	Protein	Elastic net Beta	Beta 95% CI (lower)	Beta 95% CI (upper)	Elastic net p (uncorrected)	Elastic net p (FDR-BH corrected)	ACME	ACME se	ACME p (uncorrected)	ACME 95% CI (lower)	ACME 95% CI (upper)	ADE	ADE se	ADE p (uncorrected)	ADE 95% CI (lower)	ADE 95% CI (upper)	Total	Total se	Total p (uncorrected)	Total 95% CI (lower)	Total 95% CI (upper)	p (ACME FDR BH corrected)	p (ADE FDR BH corrected)	p (Total FDR BH corrected)
Anterior Cingulate Gyrus	Syntaxin-3	0.411	0.120	0.703	0.007	0.007	0.033	0.041	0.424	−0.048	0.113	0.379	0.126	0.003	0.132	0.626	0.411	0.130	0.002	0.157	0.666	0.424	0.003	0.002
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Synapsin-3	−0.309	−0.522	−0.096	0.019	0.024	−0.022	0.024	0.359	−0.068	0.025	−0.209	0.026	1.55e-15	−0.261	−0.158	−0.231	0.035	3.12e-11	−0.299	−0.163	0.479	1.62e-15	3.25e-11
Dorsolateral Prefrontal Cortex – Middle Frontal Gyrus	Synaptotagmin-7	−0.178	−0.340	−0.016	0.039	0.044	0.032	0.024	0.178	−0.015	0.079	−0.185	0.026	2.57e-12	−0.237	−0.133	−0.153	0.035	9.31e-06	−0.221	−0.085	0.427	2.57e-12	9.31e-06
Dorsolateral Prefrontal Cortex – Superior Frontal Gyrus	Syntaxin-1A	0.521	0.263	0.780	2.86e-04	2.86e-04	0.004	0.047	0.929	−0.089	0.097	0.517	0.124	3.24e-05	0.273	0.761	0.521	0.115	5.92e-06	0.296	0.747	0.929	3.24e-05	5.92e-06
Fusiform Gyrus	Syntaxin-1A	0.482	0.189	0.776	0.002	0.002	−0.034	0.059	0.564	−0.149	0.081	0.848	0.195	1.40e-05	0.465	1.231	0.814	0.202	5.49e-05	0.419	1.210	0.943	6.79e-05	2.75e-04
Fusiform Gyrus	Secretogranin-1	1.296	0.656	1.936	0.005	0.024	−0.054	0.054	0.324	−0.160	0.053	0.680	0.158	1.70e-05	0.370	0.990	0.627	0.161	9.97e-05	0.311	0.942	0.925	6.79e-05	3.19e-04
Fusiform Gyrus	Thy-1 membrane glycoprotein	2.314	1.167	3.462	0.005	0.024	0.054	0.088	0.544	−0.120	0.227	0.848	0.292	0.004	0.276	1.420	0.902	0.301	0.003	0.311	1.492	0.943	0.006	0.005
Fusiform Gyrus	Neuronal pentraxin-1	−1.330	−2.037	−0.623	0.006	0.024	0.001	0.056	0.990	−0.108	0.110	−0.513	0.196	0.009	−0.897	−0.130	−0.513	0.203	0.012	−0.911	−0.114	0.990	0.012	0.017
Fusiform Gyrus	14-3-3 protein beta/alpha	−11.419	−17.742	−5.096	0.007	0.024	0.304	0.528	0.566	−0.732	1.339	−5.463	1.757	0.002	−8.907	−2.020	−5.160	1.817	0.005	−8.721	−1.599	0.943	0.003	0.007
Fusiform Gyrus	Synaptogyrin-3	1.316	0.577	2.055	0.008	0.024	0.016	0.056	0.779	−0.094	0.125	0.773	0.194	6.76e-05	0.393	1.154	0.789	0.202	9.04e-05	0.394	1.184	0.948	1.93e-04	3.19e-04
Fusiform Gyrus	14-3-3 protein theta	2.127	0.845	3.409	0.010	0.024	0.081	0.108	0.453	−0.130	0.292	0.790	0.343	0.021	0.119	1.462	0.871	0.353	0.014	0.180	1.562	0.943	0.025	0.017
Fusiform Gyrus	Glutamate receptor 4	1.180	0.466	1.894	0.010	0.024	−0.069	0.068	0.308	−0.202	0.064	0.452	0.195	0.020	0.070	0.833	0.383	0.198	0.053	−0.005	0.770	0.925	0.025	0.059
Fusiform Gyrus	14-3-3 protein gamma	5.777	2.227	9.327	0.011	0.024	−0.097	0.287	0.735	−0.659	0.465	3.079	0.990	0.002	1.140	5.019	2.983	1.027	0.004	0.970	4.995	0.948	0.003	0.006
Fusiform Gyrus	Neuronal pentraxin receptor	−2.822	−4.611	−1.034	0.012	0.024	−0.014	0.145	0.924	−0.298	0.270	−1.694	0.510	8.84e-04	−2.693	−0.696	−1.708	0.530	0.001	−2.746	−0.670	0.973	0.002	0.003
Fusiform Gyrus	Synapsin-3	−0.740	−1.255	−0.225	0.020	0.035	0.016	0.054	0.770	−0.091	0.122	−0.731	0.188	1.04e-04	−1.100	−0.362	−0.715	0.196	2.56e-04	−1.098	−0.332	0.948	2.61e-04	5.70e-04
Fusiform Gyrus	Gamma-synuclein	−1.346	−2.307	−0.386	0.021	0.035	−0.229	0.155	0.140	−0.534	0.075	−0.804	0.296	0.007	−1.383	−0.224	−1.033	0.273	1.52e-04	−1.567	−0.498	0.925	0.009	3.79e-04
Fusiform Gyrus	Calsyntenin-3	−0.358	−0.629	−0.086	0.012	0.036	−0.005	0.032	0.879	−0.068	0.058	−0.591	0.112	1.36e-07	−0.811	−0.371	−0.596	0.117	3.15e-07	−0.824	−0.368	0.973	1.36e-06	5.44e-06
Fusiform Gyrus	Secretogranin-3	0.607	0.160	1.054	0.020	0.036	−0.108	0.070	0.126	−0.246	0.030	0.595	0.121	9.47e-07	0.357	0.834	0.488	0.107	5.47e-06	0.278	0.698	0.925	6.31e-06	3.64e-05
Fusiform Gyrus	Synaptosomal-associated protein 25	0.553	0.142	0.964	0.023	0.037	−0.068	0.053	0.204	−0.172	0.037	0.384	0.129	0.003	0.131	0.637	0.316	0.128	0.013	0.066	0.566	0.925	0.005	0.017
Fusiform Gyrus	14-3-3 protein sigma	0.634	0.144	1.125	0.026	0.039	−0.190	0.120	0.114	−0.427	0.046	0.770	0.184	2.69e-05	0.411	1.130	0.580	0.150	1.11e-04	0.286	0.874	0.925	8.98e-05	3.19e-04
Fusiform Gyrus	Synaptic vesicle glycoprotein 2A	0.616	0.157	1.075	0.029	0.047	−0.012	0.050	0.806	−0.111	0.086	0.927	0.176	1.33e-07	0.582	1.271	0.915	0.183	5.44e-07	0.557	1.272	0.948	1.36e-06	5.44e-06
Inferior Parietal Lobule – Supramarginal Gyrus	Syntaxin-1A	0.426	0.089	0.763	0.015	0.015	0.020	0.044	0.645	−0.067	0.108	0.406	0.156	0.009	0.101	0.711	0.426	0.150	0.004	0.132	0.720	0.645	0.009	0.004
Inferior Parietal Lobule – Angular Gyrus	Syntaxin-3	0.390	0.070	0.710	0.019	0.019	−0.002	0.036	0.965	−0.073	0.070	0.391	0.147	0.008	0.103	0.679	0.390	0.142	0.006	0.111	0.669	0.965	0.008	0.006
Lateral Temporal Cortex – Middle Temporal Gyrus	Syntaxin-1A	0.467	0.186	0.748	0.002	0.002	−0.031	0.049	0.520	−0.127	0.064	0.541	0.155	4.70e-04	0.238	0.844	0.510	0.149	6.15e-04	0.218	0.801	0.801	0.003	0.004
Lateral Temporal Cortex – Superior Temporal Gyrus	Glutamate receptor 4	3.795	2.093	5.496	0.011	0.035	−0.035	0.082	0.670	−0.196	0.126	1.352	0.368	2.42e-04	0.630	2.074	1.317	0.375	4.51e-04	0.581	2.052	0.779	0.003	0.003
Lateral Temporal Cortex – Superior Temporal Gyrus	Thy-1 membrane glycoprotein	4.454	2.428	6.480	0.011	0.035	−0.057	0.092	0.534	−0.238	0.123	1.338	0.381	4.53e-04	0.590	2.086	1.281	0.387	9.37e-04	0.522	2.039	0.739	0.003	0.004
Lateral Temporal Cortex – Superior Temporal Gyrus	Alpha-synuclein	−3.817	−5.567	−2.066	0.011	0.035	0.113	0.124	0.364	−0.131	0.357	−0.975	0.415	0.019	−1.788	−0.161	−0.862	0.414	0.037	−1.673	−0.050	0.739	0.029	0.052
Lateral Temporal Cortex – Superior Temporal Gyrus	Tenascin-R	−2.802	−4.133	−1.471	0.012	0.035	−0.021	0.068	0.757	−0.153	0.112	−0.857	0.312	0.006	−1.469	−0.246	−0.878	0.318	0.006	−1.502	−0.255	0.785	0.015	0.015
Lateral Temporal Cortex – Superior Temporal Gyrus	14-3-3 protein beta/alpha	−14.758	−21.844	−7.671	0.012	0.035	0.285	0.350	0.416	−0.402	0.971	−3.552	1.281	0.006	−6.063	−1.041	−3.268	1.288	0.011	−5.793	−0.743	0.739	0.015	0.025
Lateral Temporal Cortex – Superior Temporal Gyrus	Secretogranin-3	1.934	1.002	2.866	0.012	0.035	−0.130	0.115	0.256	−0.355	0.094	0.608	0.246	0.014	0.125	1.090	0.477	0.228	0.036	0.031	0.924	0.739	0.024	0.052
Lateral Temporal Cortex – Superior Temporal Gyrus	14-3-3 protein epsilon	12.475	6.197	18.753	0.013	0.035	−0.135	0.281	0.631	−0.686	0.416	2.893	1.236	0.019	0.471	5.316	2.758	1.258	0.028	0.292	5.225	0.779	0.029	0.051
Lateral Temporal Cortex – Superior Temporal Gyrus	14-3-3 protein eta	4.282	2.091	6.472	0.014	0.035	−0.249	0.225	0.269	−0.690	0.192	1.442	0.531	0.007	0.401	2.482	1.193	0.503	0.018	0.208	2.178	0.739	0.015	0.035
Lateral Temporal Cortex – Superior Temporal Gyrus	Syntaxin-3	4.388	2.043	6.733	0.015	0.035	0.060	0.095	0.530	−0.127	0.247	1.330	0.394	7.36e-04	0.558	2.103	1.390	0.400	5.05e-04	0.607	2.173	0.739	0.003	0.003
Lateral Temporal Cortex – Superior Temporal Gyrus	Syntaxin-7	−4.895	−7.601	−2.189	0.016	0.035	0.048	0.121	0.693	−0.190	0.286	−1.240	0.549	0.024	−2.316	−0.165	−1.192	0.559	0.033	−2.288	−0.096	0.779	0.033	0.052
Lateral Temporal Cortex – Superior Temporal Gyrus	Synaptotagmin-2	1.771	0.777	2.764	0.017	0.035	0.038	0.056	0.491	−0.071	0.148	0.803	0.223	3.07e-04	0.367	1.239	0.842	0.225	1.87e-04	0.400	1.283	0.739	0.003	0.003
Lateral Temporal Cortex – Superior Temporal Gyrus	Vesicle-associated membrane protein 2	1.451	0.609	2.293	0.018	0.035	0.056	0.067	0.400	−0.075	0.187	0.639	0.238	0.007	0.172	1.105	0.695	0.239	0.004	0.227	1.163	0.739	0.015	0.011
Lateral Temporal Cortex – Superior Temporal Gyrus	Synapsin-3	0.882	0.307	1.458	0.022	0.039	−0.010	0.038	0.785	−0.086	0.065	0.552	0.178	0.002	0.203	0.901	0.542	0.182	0.003	0.186	0.897	0.785	0.007	0.010
Cuneus	Syntaxin-1A	0.418	0.116	0.720	0.008	0.008	0.007	0.035	0.851	−0.063	0.076	0.652	0.132	7.92e-07	0.393	0.910	0.658	0.137	1.42e-06	0.391	0.926	0.851	1.58e-06	2.84e-06
Cuneus	Gamma-synuclein	−0.589	−0.970	−0.207	0.004	0.038	0.028	0.042	0.502	−0.054	0.110	−0.525	0.143	2.46e-04	−0.805	−0.244	−0.497	0.147	7.24e-04	−0.785	−0.209	0.851	2.46e-04	7.24e-04
Posterior Cingulate Gyrus	Syntaxin-1A	0.424	0.134	0.713	0.006	0.006	−0.000	0.004	0.996	−0.008	0.008	0.407	0.120	6.95e-04	0.172	0.642	0.407	0.120	6.90e-04	0.172	0.641	0.997	0.001	0.001
Posterior Cingulate Gyrus	Calsyntenin-3	−0.284	−0.558	−0.010	0.043	0.043	0.000	0.000	0.997	−0.001	0.001	−0.284	0.120	0.018	−0.518	−0.050	−0.284	0.120	0.018	−0.518	−0.050	0.997	0.018	0.018
Precuneus	Syntaxin-1A	0.499	0.201	0.796	0.002	0.002	0.020	0.044	0.659	−0.067	0.107	0.479	0.139	5.62e-04	0.207	0.751	0.499	0.132	1.66e-04	0.239	0.758	0.659	5.62e-04	1.66e-04
Caudate Nucleus	Neuronal pentraxin receptor	0.497	0.116	0.879	0.012	0.012	0.006	0.018	0.739	−0.030	0.042	0.494	0.157	0.002	0.186	0.802	0.500	0.158	0.001	0.192	0.809	0.901	0.003	0.003
Caudate Nucleus	Calsyntenin-3	−0.490	−0.827	−0.154	0.006	0.030	−0.002	0.014	0.901	−0.029	0.026	−0.342	0.143	0.017	−0.623	−0.061	−0.343	0.144	0.017	−0.626	−0.061	0.901	0.017	0.017

Region	Protein	Elastic net Beta	Beta 95% CI (lower)	Beta 95% CI (upper)	Elastic net p (uncorrected)	Elastic net p (FDR-BH corrected)	ACME	ACME se	ACME p (uncorrected)	ACME 95% CI (lower)	ACME 95% CI (upper)	ADE	ADE se	ADE p (uncorrected)	ADE 95% CI (lower)	ADE 95% CI (upper)	Total	Total se	Total p (uncorrected)	Total 95% CI (lower)	Total 95% CI (upper)	p (ACME FDR BH corrected)	p (ADE FDR BH corrected)	p (Total FDR BH corrected)
Putamen	14-3-3 protein eta	0.446	0.134	0.758	0.007	0.007	0.027	0.036	0.455	−0.044	0.098	0.419	0.137	0.002	0.150	0.688	0.446	0.139	0.001	0.174	0.718	0.455	0.002	0.001
Superior Parietal Lobule	Syntaxin-1A	0.499	0.219	0.778	0.001	0.001	0.027	0.054	0.618	−0.078	0.132	0.452	0.123	2.29e-04	0.211	0.692	0.478	0.111	1.65e-05	0.261	0.696	0.679	4.59e-04	3.29e-05
Superior Parietal Lobule	Calsyntenin-3	−0.416	−0.689	−0.143	0.004	0.027	−0.007	0.016	0.679	−0.039	0.025	−0.328	0.111	0.003	−0.546	−0.110	−0.335	0.111	0.003	−0.552	−0.117	0.679	0.003	0.003

Supplementary Table S8. Pairwise intercorrelations among synaptic proteins: Spearman's correlation coefficients (ρ).

Protein	Syntaxin-3	Synapsin-3	Synaptotagmin-7	Syntaxin-1A	Secretogranin-1	Thy-1 membrane glycoprotein	Neuronal pentraxin-1	14-3-3 protein beta/alpha	Synaptogyrin-3	14-3-3 protein theta	Glutamate receptor 4	14-3-3 protein gamma	Neuronal pentraxin receptor	Gamma-synuclein	Calsyntenin-3	Secretogranin-3	Synaptosomal-associated protein 25	14-3-3 protein sigma	Synaptic vesicle glycoprotein 2A	Alpha-synuclein	Tenascin-R	14-3-3 protein epsilon	14-3-3 protein eta	Syntaxin-7	Synaptotagmin-2	Vesicle-associated membrane protein 2
Syntaxin-3	1	-0.03	-0.15	0.86	0.529	-0.191	0.463	0.634	-0.038	0.693	0.577	0.635	0.619	0.668	-0.001	-0.243	-0.369	0.497	0.706	0.203	0.702	0.657	0.798	0.697	-0.082	0.559
Synapsin-3	-0.03	1	0.381	-0.085	-0.381	-0.476	-0.446	-0.182	0.194	0.114	-0.005	-0.148	-0.299	-0.218	-0.282	0.18	-0.391	0.051	-0.287	0.575	-0.336	-0.045	-0.141	-0.206	-0.514	-0.278
Synaptotagmin-7	-0.15	0.381	1	-0.309	-0.209	-0.291	-0.202	-0.530	-0.207	-0.276	0.003	-0.434	-0.393	-0.379	-0.437	0.032	-0.126	-0.253	-0.328	0.178	-0.185	-0.396	-0.344	-0.381	-0.293	-0.513
Syntaxin-1A	0.86	-0.085	-0.309	1	0.493	-0.071	0.532	0.746	0.067	0.622	0.495	0.722	0.716	0.743	0.09	-0.113	-0.203	0.385	0.758	0.178	0.519	0.737	0.827	0.791	0.046	0.684
Secretogranin-1	0.529	-0.381	-0.209	0.493	1	0.212	0.649	0.512	-0.276	0.371	0.232	0.471	0.507	0.475	0.15	-0.065	-0.133	0.262	0.417	-0.027	0.425	0.505	0.512	0.386	0.018	0.158
Thy-1 membrane glycoprotein	-0.191	-0.476	-0.291	-0.071	0.212	1	0.198	0.025	0.056	-0.377	-0.551	0.021	0.074	-0.032	0.236	0.076	0.245	-0.339	-0.049	-0.278	-0.071	-0.119	-0.069	0.076	0.139	0.160
Neuronal pentraxin-1	0.463	-0.446	-0.202	0.532	0.649	0.198	1	0.388	0.026	0.311	0.434	0.364	0.557	0.417	0.083	-0.002	0.048	0.256	0.319	-0.264	0.61	0.322	0.362	0.45	0.214	0.230
14-3-3 protein beta/alpha	0.634	-0.182	-0.53	0.746	0.512	0.025	0.388	1	-0.063	0.689	0.316	0.933	0.573	0.748	0.323	-0.312	-0.179	0.537	0.677	0.017	0.385	0.942	0.861	0.807	0.112	0.694
Synaptogyrin-3	-0.038	0.194	-0.207	0.067	-0.276	0.056	0.026	-0.063	1	-0.134	-0.301	-0.122	-0.071	0.011	0.046	0.202	-0.195	-0.018	-0.164	-0.158	-0.126	-0.153	-0.088	0.072	0.11	0.206
14-3-3 protein theta	0.693	0.114	-0.276	0.622	0.371	-0.377	0.311	0.689	-0.134	1	0.604	0.681	0.322	0.578	0.319	-0.273	-0.246	0.657	0.422	0.098	0.41	0.687	0.737	0.584	-0.163	0.365
Glutamate receptor 4	0.577	-0.005	0.003	0.495	0.232	-0.551	0.434	0.316	-0.301	0.604	1	0.344	0.422	0.329	-0.018	-0.21	-0.125	0.348	0.387	0.058	0.579	0.377	0.410	0.335	-0.076	-0.013
14-3-3 protein gamma	0.635	-0.148	-0.434	0.722	0.471	0.021	0.364	0.933	-0.122	0.681	0.344	1	0.605	0.768	0.202	-0.303	-0.335	0.491	0.662	-0.051	0.409	0.894	0.897	0.797	-0.025	0.764
Neuronal pentraxin receptor	0.619	-0.299	-0.393	0.716	0.507	0.074	0.557	0.573	-0.071	0.322	0.422	0.605	1	0.546	-0.069	0.115	-0.140	0.278	0.6	0.109	0.477	0.634	0.658	0.503	0.005	0.517
Gamma-synuclein	0.668	-0.218	-0.379	0.743	0.475	-0.032	0.417	0.748	0.011	0.578	0.329	0.768	0.546	1	0.133	-0.314	-0.187	0.470	0.761	-0.003	0.387	0.709	0.806	0.893	0.086	0.759
Calsyntenin-3	-0.001	-0.282	-0.437	0.09	0.15	0.236	0.083	0.323	0.046	0.319	-0.018	0.202	-0.069	0.133	1	-0.21	0.295	0.159	0.159	-0.334	0.089	0.153	0.087	0.33	0.215	0.190
Secretogranin-3	-0.243	0.18	0.032	-0.113	-0.065	0.076	-0.002	-0.312	0.202	-0.273	-0.21	-0.303	0.115	-0.314	-0.21	1	-0.129	-0.428	-0.357	0.341	-0.315	-0.147	-0.227	-0.422	-0.29	-0.299
Synaptosomal-associated protein 25	-0.369	-0.391	-0.126	-0.203	-0.133	0.245	0.048	-0.179	-0.195	-0.246	-0.125	-0.335	-0.140	-0.187	0.295	-0.129	1	-0.373	-0.138	-0.149	-0.198	-0.276	-0.291	-0.105	0.474	-0.210
14-3-3 protein sigma	0.497	0.051	-0.253	0.385	0.262	-0.339	0.256	0.537	-0.018	0.657	0.348	0.491	0.278	0.47	0.159	-0.428	-0.373	1	0.299	-0.118	0.3	0.479	0.406	0.487	-0.01	0.515
Synaptic vesicle glycoprotein 2A	0.706	-0.287	-0.328	0.758	0.417	-0.049	0.319	0.677	-0.164	0.422	0.387	0.662	0.600	0.761	0.159	-0.357	-0.138	0.299	1	0.004	0.592	0.647	0.726	0.814	0.321	0.710
Alpha-synuclein	0.203	0.575	0.178	0.178	-0.027	-0.278	-0.264	0.017	-0.158	0.098	0.058	-0.051	0.109	-0.003	-0.334	0.341	-0.149	-0.118	0.004	1	-0.224	0.200	0.117	-0.161	-0.365	-0.178
Tenascin-R	0.702	-0.336	-0.185	0.519	0.425	-0.071	0.610	0.385	-0.126	0.410	0.579	0.409	0.477	0.387	0.089	-0.315	-0.198	0.300	0.592	-0.224	1	0.340	0.498	0.465	0.171	0.359
14-3-3 protein epsilon	0.657	-0.045	-0.396	0.737	0.505	-0.119	0.322	0.942	-0.153	0.687	0.377	0.894	0.634	0.709	0.153	-0.147	-0.276	0.479	0.647	0.2	0.34	1	0.872	0.709	-0.056	0.624
14-3-3 protein eta	0.798	-0.141	-0.344	0.827	0.512	-0.069	0.362	0.861	-0.088	0.737	0.41	0.897	0.658	0.806	0.087	-0.227	-0.291	0.406	0.726	0.117	0.498	0.872	1	0.778	-0.111	0.751
Syntaxin-7	0.697	-0.206	-0.381	0.791	0.386	0.076	0.450	0.807	0.072	0.584	0.335	0.797	0.503	0.893	0.33	-0.422	-0.105	0.487	0.814	-0.161	0.465	0.709	0.778	1	0.144	0.793
Synaptotagmin-2	-0.082	-0.514	-0.293	0.046	0.018	0.139	0.214	0.112	0.11	-0.163	-0.076	-0.025	0.005	0.086	0.215	-0.29	0.474	-0.010	0.321	-0.365	0.171	-0.056	-0.111	0.144	1	0.218
Vesicle-associated membrane protein 2	0.559	-0.278	-0.513	0.684	0.158	0.16	0.230	0.694	0.206	0.365	-0.013	0.764	0.517	0.759	0.19	-0.299	-0.210	0.515	0.71	-0.178	0.359	0.624	0.751	0.793	0.218	1

Supplementary Table S9. Pairwise intercorrelations among synaptic proteins: Benjamini–Hochberg FDR-corrected p-values for the correlations in Supplementary Table S8.

Protein	Syntaxin-3	Synapsin-3	Synaptotagmin-7	Syntaxin-1A	Secretogranin-1	Thy-1 membrane glycoprotein	Neuronal pentraxin-1	14-3-3 protein beta/alpha	Synaptogyrin-3	14-3-3 protein theta	Glutamate receptor 4	14-3-3 protein gamma	Neuronal pentraxin receptor	Gamma-synuclein	Calsyntenin-3	Secretogranin-3	Synaptosomal-associated protein 25	14-3-3 protein sigma	Synaptic vesicle glycoprotein 2A	Alpha-synuclein	Tenascin-R	14-3-3 protein epsilon	14-3-3 protein eta	Syntaxin-7	Synaptotagmin-2	Vesicle-associated membrane protein 2
Syntaxin-3	0	0.933	0.583	8.83e-08	0.014	0.469	0.039	0.001	0.909	2.51e-04	0.006	0.001	0.002	5.51e-04	0.997	0.347	0.138	0.050	1.73e-04	0.454	1.92e-04	7.25e-04	4.87e-06	2.21e-04	0.783	0.011
Synapsin-3	0.933	0	0.097	0.779	0.097	0.028	0.045	0.484	0.464	0.678	0.994	0.583	0.209	0.402	0.243	0.491	0.100	0.876	0.242	0.007	0.156	0.876	0.616	0.438	0.015	0.280
Synaptotagmin-7	0.583	0.097	0	0.201	0.413	0.213	0.431	0.010	0.427	0.244	0.994	0.048	0.080	0.094	0.046	0.921	0.653	0.372	0.164	0.509	0.469	0.077	0.155	0.097	0.212	0.020
Syntaxin-1A	8.83e-08	0.779	0.201	0	0.025	0.807	0.013	4.61e-05	0.820	0.002	0.027	1.05e-04	1.26e-04	5.18e-05	0.763	0.688	0.463	0.156	2.94e-05	0.515	0.016	6.28e-05	1.17e-06	6.93e-06	0.876	5.79e-04
Secretogranin-1	0.014	0.097	0.413	0.025	0	0.404	5.53e-04	0.014	0.254	0.100	0.364	0.027	0.015	0.026	0.571	0.818	0.629	0.348	0.063	0.938	0.053	0.015	0.018	0.094	0.962	0.571
Thy-1 membrane glycoprotein	0.469	0.028	0.213	0.807	0.404	0	0.439	0.938	0.847	0.096	0.007	0.952	0.794	0.921	0.343	0.794	0.343	0.191	0.870	0.260	0.806	0.657	0.812	0.794	0.598	0.570
Neuronal pentraxin-1	0.039	0.045	0.431	0.013	5.53e-04	0.439	0	0.086	0.938	0.175	0.051	0.109	0.006	0.059	0.772	0.994	0.876	0.364	0.174	0.292	0.002	0.164	0.129	0.042	0.402	0.395
14-3-3 protein beta/alpha	0.001	0.484	0.010	4.61e-05	0.014	0.938	0.086	0	0.823	1.73e-04	0.175	3.72e-12	0.004	2.14e-05	0.164	0.175	0.506	0.022	3.07e-04	0.963	0.088	8.60e-13	8.83e-08	2.27e-06	0.678	3.15e-04
Synaptogyrin-3	0.909	0.464	0.427	0.820	0.254	0.847	0.938	0.823	0	0.619	0.214	0.657	0.807	0.978	0.876	0.438	0.469	0.963	0.551	0.571	0.641	0.571	0.771	0.807	0.689	0.454
14-3-3 protein theta	2.51e-04	0.678	0.244	0.002	0.100	0.096	0.175	1.73e-04	0.619	0	0.002	2.10e-04	0.164	0.003	0.166	0.252	0.343	0.002	0.059	0.737	0.063	1.81e-04	6.28e-05	0.004	0.535	0.134
Glutamate receptor 4	0.006	0.994	0.994	0.027	0.364	0.007	0.051	0.175	0.214	0.002	0	0.144	0.059	0.164	0.962	0.418	0.658	0.175	0.097	0.847	0.004	0.100	0.084	0.164	0.794	0.976
14-3-3 protein gamma	0.001	0.583	0.048	1.05e-04	0.027	0.952	0.109	3.72e-12	0.657	2.10e-04	0.144	0	0.002	9.25e-06	0.431	0.191	0.164	0.042	5.04e-04	0.869	0.064	1.35e-09	2.75e-09	3.40e-06	0.938	3.25e-05
Neuronal pentraxin receptor	0.002	0.209	0.080	1.26e-04	0.015	0.794	0.006	0.004	0.807	0.164	0.059	0.002	0	0.007	0.807	0.672	0.610	0.309	0.002	0.698	0.025	8.17e-04	7.19e-04	0.018	0.994	0.019
Gamma-synuclein	5.51e-04	0.402	0.094	5.18e-05	0.026	0.921	0.059	2.14e-05	0.978	0.003	0.164	9.25e-06	0.007	0	0.616	0.174	0.482	0.054	1.83e-05	0.994	0.086	8.84e-05	3.40e-06	2.51e-09	0.765	4.04e-05
Calsyntenin-3	0.997	0.243	0.046	0.763	0.571	0.343	0.772	0.164	0.876	0.166	0.962	0.431	0.807	0.616	0	0.410	0.227	0.592	0.556	0.164	0.757	0.567	0.771	0.164	0.401	0.482
Secretogranin-3	0.347	0.491	0.921	0.688	0.818	0.794	0.994	0.175	0.438	0.252	0.418	0.191	0.672	0.174	0.410	0	0.641	0.088	0.128	0.157	0.173	0.577	0.393	0.059	0.214	0.229
Synaptosomal-associated protein 25	0.138	0.100	0.653	0.463	0.629	0.343	0.876	0.506	0.469	0.343	0.658	0.164	0.610	0.482	0.227	0.641	0	0.166	0.623	0.601	0.454	0.261	0.256	0.718	0.033	0.454
14-3-3 protein sigma	0.050	0.876	0.372	0.156	0.348	0.191	0.364	0.022	0.963	0.002	0.175	0.042	0.309	0.054	0.592	0.088	0.166	0	0.275	0.715	0.260	0.049	0.130	0.050	0.984	0.046
Synaptic vesicle glycoprotein 2A	1.73e-04	0.242	0.164	2.94e-05	0.063	0.870	0.174	3.07e-04	0.551	0.059	0.097	5.04e-04	0.002	1.83e-05	0.556	0.128	0.623	0.275	0	0.994	0.003	7.25e-04	8.84e-05	2.28e-06	0.173	2.63e-04
Alpha-synuclein	0.454	0.007	0.509	0.515	0.938	0.260	0.292	0.963	0.571	0.737	0.847	0.869	0.698	0.994	0.164	0.157	0.601	0.715	0.994	0	0.399	0.454	0.682	0.567	0.126	0.540
Tenascin-R	1.92e-04	0.156	0.469	0.016	0.053	0.806	0.002	0.088	0.641	0.063	0.004	0.064	0.025	0.086	0.757	0.173	0.454	0.260	0.003	0.399	0	0.143	0.023	0.033	0.509	0.141
14-3-3 protein epsilon	7.25e-04	0.876	0.077	6.28e-05	0.015	0.657	0.164	8.60e-13	0.571	1.81e-04	0.100	1.35e-09	8.17e-04	8.84e-05	0.567	0.577	0.261	0.049	7.25e-04	0.454	0.143	0	3.83e-08	1.16e-04	0.847	0.002
14-3-3 protein eta	4.87e-06	0.616	0.155	1.17e-06	0.018	0.812	0.129	8.83e-08	0.771	6.28e-05	0.084	2.75e-09	7.19e-04	3.40e-06	0.771	0.393	0.256	0.130	8.84e-05	0.682	0.023	3.83e-08	0	1.20e-05	0.689	7.25e-05
Syntaxin-7	2.21e-04	0.438	0.097	6.93e-06	0.094	0.794	0.042	2.27e-06	0.807	0.004	0.164	3.40e-06	0.018	2.51e-09	0.164	0.059	0.718	0.050	2.28e-06	0.567	0.033	1.16e-04	1.20e-05	0	0.592	9.25e-06
Synaptotagmin-2	0.783	0.015	0.212	0.876	0.962	0.598	0.402	0.678	0.689	0.535	0.794	0.938	0.994	0.765	0.401	0.214	0.033	0.984	0.173	0.126	0.509	0.847	0.689	0.592	0	0.418
Vesicle-associated membrane protein 2	0.011	0.280	0.020	5.79e-04	0.571	0.570	0.395	3.15e-04	0.454	0.134	0.976	3.25e-05	0.019	4.04e-05	0.482	0.229	0.454	0.046	2.63e-04	0.540	0.141	0.002	7.25e-05	9.25e-06	0.418	0