

Supplementary Material

eTable 1. The 52 cortical proteotypic peptides related to residual cognitive decline i.e., were associated with annual rate of cognitive decline controlling for ten neuropathologic brain indices. A positive estimate indicates an association of slower cognitive decline with a higher level of the protein (the top 31 peptides listed in the table and highlighted in blue), while a negative estimate indicates an association of a lower level of the protein with slower cognitive decline (the bottom 21 peptides listed in the table and highlighted in pink).

	Peptides	Estimates	p-value	SE
1	VGf_1	0.031	<0.001	0.005
2	VGf_2	0.033	<0.001	0.005
3	SYT12_1	0.039	<0.001	0.007
4	STX1A_1	0.060	<0.001	0.013
5	CD47_1	0.091	0.001	0.022
6	NDUFA7_2	0.036	0.002	0.009
7	NDUFS6_1	0.037	0.003	0.010
8	tau_AT8	0.036	0.003	0.010
9	SNAP25_2	0.045	0.003	0.013
10	NDUFA7_1	0.046	0.003	0.013
11	STXBPI_6	0.031	0.003	0.009
12	SNAP25_1	0.035	0.005	0.010
13	NDUFA10_2	0.043	0.007	0.013
14	tau_AT100	0.063	0.009	0.020
15	ITPK1_1	0.030	0.009	0.010
16	SYT7_2	0.029	0.009	0.009
17	NDUFS6_2	0.036	0.009	0.013
18	SNAP25_4	0.030	0.009	0.010
19	UQCR10_2	0.043	0.009	0.014
20	STX1A_2	0.032	0.010	0.013
21	CD47_2	0.049	0.011	0.017
22	NDUFA6_2	0.038	0.011	0.013
23	NDUFV1_2	0.033	0.012	0.011
24	UQCRC2_2	0.038	0.015	0.013
25	UQCRC2_1	0.038	0.021	0.014
26	VAPB_2	0.055	0.025	0.021
27	ND UFA5_1	0.034	0.032	0.013
28	SNAP25_3	0.024	0.034	0.010
29	BIN1_4	0.040	0.036	0.016
30	SNAP25_6	0.018	0.038	0.008
31	NDUFV1_1	0.028	0.049	0.013
32	tau_12E8_s262	-0.012	<0.001	0.002
33	IGFBP5_1	-0.026	<0.001	0.005
34	tau_AT100_t217	-0.020	<0.001	0.004
35	AMPD2_2	-0.042	0.001	0.011
36	GSTP1_1	-0.033	0.004	0.010
37	CLU_2	-0.028	0.007	0.009
38	PTMS_1	-0.034	0.007	0.010
39	HSPB2_2	-0.018	0.009	0.006
40	C9orf16_2	-0.023	0.011	0.008
41	AK4_2	-0.041	0.011	0.014
42	RUVBL1_2	-0.045	0.017	0.016
43	FYN_3	-0.048	0.031	0.019
44	TPRG1L_1	-0.024	0.033	0.009
45	tau_77G7_s305	-0.006	0.033	0.002
46	AK4_1	-0.032	0.038	0.013
47	SLC6A12_1	-0.021	0.038	0.009
48	VAMP5_1	-0.015	0.038	0.006
49	VAT1_2	-0.014	0.043	0.006
50	SYN2_2	-0.021	0.0091	0.009
51	GRB2_2	-0.042	0.018	0.018
52	GFAP_1	-0.009	0.004	0.004

Note. Each row is the result of a separate linear mixed-effects model that included terms for demographics (age before death, sex, and education), and ten neuropathologic brain indices, and that displays the strength of the association between each protein and annual cognitive decline. The results are ordered by strength of the association (strongest at the top) and by their association with cognitive decline (proteins associated with slower cognitive decline in blue and proteins associated with faster cognitive decline in pink). All p-values were FDR corrected at 5%.

eTable 2. The means and range of variances 52 cortical proteotypic peptides related to residual cognitive decline i.e., were associated with annual rate of cognitive decline controlling for ten neuropathologic brain indices.

	Peptides	Mean	Range	
			Minimum	Maximum
1	VGF_1	-0.044	3.290	1.640
2	VGF_2	-0.037	-2.790	1.570
3	SYT12_1	-0.041	-2.780	1.000
4	STX1A_1	-0.028	-1.830	0.564
5	CD47_1	-0.001	-1.190	0.527
6	NDUFA7_2	-0.021	-5.800	1.330
7	NDUFS6_1	-0.013	-2.710	1.350
8	tau_AT8	-0.015	-1.640	0.804
9	SNAP25_2	-0.015	-3.610	0.509
10	NDUFA7_1	0.014	-1.340	0.594
11	STXBPI_6	-0.021	-2.110	0.916
12	SNAP25_1	-0.019	-2.170	0.742
13	NDUFA10_2	-0.015	-1.540	0.865
14	tau_AT100	-0.004	-1.700	0.903
15	ITPK1_1	-0.022	-1.630	0.891
16	SYT7_2	-0.018	-1.160	0.857
17	NDUFS6_2	-0.021	-3.530	0.586
18	SNAP25_4	-0.015	-2.690	0.839
19	UQCRC10_2	-0.018	-1.250	0.508
20	STX1A_2	-0.012	-2.190	0.810
21	CD47_2	-0.009	-1.240	0.605
22	NDUFA6_2	-0.010	-1.170	1.880
23	NDUFV1_2	-0.023	-3.040	0.671
24	UQCRC2_2	-0.017	-1.270	0.721
25	UQCRC2_1	-0.018	-1.360	0.647
26	VAPB_2	-0.007	-1.020	0.378
27	ND UFA5_1	-0.018	-1.140	0.626
28	SNAP25_3	-0.006	-2.270	1.120
29	BIN1_4	-0.015	-1.250	0.651
30	SNAP25_6	-0.010	-4.460	1.100
31	NDUFV1_1	-0.018	-1.390	0.819
32	tau_12E8_s262	0.061	-6.030	5.950
33	IGFBP5_1	-0.020	-2.680	2.230
34	tau_AT100_t217	0.073	-2.840	3.660
35	AMPD2_2	-0.003	-1.070	3.810
36	GSTP1_1	0.027	-1.340	1.570
37	CLU_2	0.016	-0.759	2.760
38	PTMS_1	-0.007	-1.490	0.930
39	HSPB2_2	-0.027	-3.420	1.610
40	C9orf16_2	-0.025	-1.950	1.030
41	AK4_2	-0.011	-1.400	0.673
42	RUVBL1_2	0.008	-0.470	2.450
43	FYN_3	0.007	-1.590	1.020
44	TPRG1L_1	-0.036	-3.290	1.010
45	tau_77G7_s305	-0.126	-5.310	4.340
46	AK4_1	-0.005	-1.070	0.691
47	SLC6A12_1	-0.008	-1.370	1.520
48	VAMP5_1	-0.031	-2.570	2.300
49	VAT1_2	0.028	-2.880	1.960
50	SYN2_2	-0.045	-2.600	0.655
51	GRB2_2	-0.001	-0.959	0.723
52	GFAP_1	-0.015	-2.870	2.610

eTable 3. Principal components analysis and component functions for the cognitive resilience proteins. The table displays a rotated solution of the factor pattern. For ease of review, factor loadings < 0.5 were suppressed and only display components that met the Kaiser's criterion of eigenvalues >1

		Rotated Factor Pattern									
	Function	1	2	3	4	5	6	7	8	9	10
NDUFS6_2	Mitochondrial	0.90									
NDUFA10_2	Mitochondrial	0.90									
NDUFA7_1	Mitochondrial	0.88									
NDUFA5_1	Mitochondrial	0.88									
NDUFV1_2	Mitochondrial	0.88									
NDUFA6_2	Mitochondrial	0.88									
NDUFV1_1	Mitochondrial	0.87									
UQCRC2_2	Mitochondrial	0.83									
UQCRC2_1	Mitochondrial	0.83									
NDUFA7_2	Mitochondrial	0.82									
NDUFS6_1	Mitochondrial	0.82									
SYT12_1	Synaptic	0.68									
UQCR10_2	Mitochondrial	0.66									
SNAP25_2	Synaptic	0.61									
STXBP1_6	Synaptic	0.61									
BIN1_4	Cell proliferation	0.54									
VAPB_2	Vesicle transportation	0.52									
SYT7_2	Synaptic										
GRB2_2	Signal transduction										
RUVBL1_2	Binding										
VAT1_2	Synaptic	-0.54									
GSTP1_1	Metabolic	-0.55									
SNAP25_4	Synaptic		0.90								
SNAP25_3	Synaptic		0.89								
SNAP25_1	Synaptic		0.82								
SNAP25_6	Synaptic		0.78								
STX1A_2	Synaptic		0.54								
tau_AT100	Synaptic			0.71							
CD47_2	Cell adhesion			0.70							
CD47_1	Cell adhesion			0.66							
SLC6A12_1	Synaptic										
AMPD2_2	Metabolic										
VEGF_2	Synaptic				0.79						
VEGF_1	Synaptic				0.78						
STX1A_1	Synaptic										
FYN_3	Cell growth										
SYN2_2	Synaptic					0.67					
PTMS_1	Cell modification					0.65					
TPRG1L_1	Synaptic					0.63					
C9orf16_2	Protein binding										
IGFBP5_1	Signaling										
tau_12E8_s262	Synaptic						0.74				
tau_77G7_s305	Synaptic						0.72				
tau_AT100_r217	Synaptic						0.64				
AK4_2	Mitochondrial							0.64			
AK4_1	Mitochondrial							0.62			
ITPK1_1	Synaptic										
GFAP_1	Communication								0.51		
tau_AT8	Synaptic									0.83	
VAMP5_1	Synaptic										0.66
HSPB2_2	Mitochondrial										
CLU_2	Protein folding										

Note. Bolded represents factor loading >0.50. Blue background represents proteins associated with slower cognitive decline and pink background represents proteins associated with faster cognitive decline.

eTable 4. One third of cognitive resilience peptides also provide resilience for motor decline and progressive parkinsonism. Additional cortical proteins may provide resilience for motor decline or progressive Parkinsonism, but not for cognitive decline.

		Motor Decline	p-value	Progressive Parkinsonism	p-value
	Protein	14/52		10/52	
1	VGF_1	0.004	0.005	-0.022	0.019
2	VGF_2	0.005	0.005	-0.029	0.003
3	SYT12_1	0.005	0.038	-0.030	0.031
4	STX1A_1	0.008	0.049	-0.060	0.019
5	NDUFA7_1	0.009	0.038		
6	STXBP1_6	0.007	0.018		
7	NDUFA10_2			-0.053	0.033
8	SYT7_2			-0.036	0.039
9	NDUFA6_2	0.011	0.028		
10	tau_12E8_s262	-0.001	0.038		
11	IGFBP5_1	-0.005	0.004	-0.036	0.039
12	AMPD2_2			0.052	0.019
13	GSTP1_1	-0.007	0.038	0.036	0.041
14	PTMS_1	-0.007	0.038		
15	HSPB2_2	-0.004	0.038		
16	FYN_3	-0.022	0.003		
17	GRB2_2	-0.016	0.018	0.07492	0.031194
1	APOE_2	0.007	0.005		
2	CD44_1	-0.002	0.045		
3	CD44_2	-0.002	0.045		
4	GFAP_1	-0.003	0.038		
5	GFAP_2	-0.003	0.038		
6	LDHA_2	0.001	0.038		
1	PADI2_1			0.019	0.044
2	PADI2_2			0.021	0.033
3	PIK3R1_1			0.006	0.030
4	RPL35A_1			0.001	0.028
5	SNAP25_7			0.015	0.044
6	SPPL1_1			0.009	0.033

Note. Each row is the result of a separate linear mixed-effects model that included terms for demographics (age before death, sex, and education), and ten neuropathologic brain indices, and that displays the strength of the association between a single cognitive resilience protein which also provides resilience for motor decline and/or progressive Parkinsonism. One-third of cognitive resilience proteins (17/52) also provide resilience for motor decline /parkinsonism. Twelve of 226 additional cortical proteins provide resilience for either motor decline or progressive Parkinsonism but not for cognitive decline. Proteins that are specific to motor decline are highlighted in orange and those proteins specific to progressive parkinsonism (in yellow). All *p*-values were FDR corrected at 5%.

eTable 5. Many of the 52 were associated with AD pathological phenotypes with AD pathology (n=47), amyloid (n=44) and tau (n=49), adjusted for demographics.

	Protein	Cognitive Decline		AD pathology		Amyloid		Tau	
			p-value	47/52	p-value	44/52	p-value	49/52	p-value
1	VEGF_1	0.061	<0.001	-0.209	<0.001	-0.511	<0.001	-0.771	<0.001
2	VEGF_2	0.064	<0.001	-0.217	<0.001	-0.532	<0.001	-0.778	<0.001
3	SYT12_1	0.066	<0.001	-0.198	0.001	-0.577	<0.001	-0.713	<0.001
4	STX1A_1	0.131	<0.001	-0.525	<0.001	-1.370	<0.001	-1.683	<0.001
5	CD47_1	0.196	<0.001	-0.711	<0.001	-2.099	<0.001	-2.621	<0.001
6	NDUFA7_2	0.049	<0.001	NS	NS	NS	NS	-0.369	0.008
7	NDUFS6_1	0.056	<0.001	-0.189	<0.001	-0.268	0.050	-0.619	<0.001
8	tau_AT8	0.073	<0.001	-0.242	<0.001	-0.464	<0.001	-0.619	<0.001
9	SNAP25_2	0.105	<0.001	-0.448	<0.001	-1.232	<0.001	-1.413	<0.001
10	NDUFA7_1	0.082	<0.001	-0.189	<0.001	-0.474	0.005	-0.841	<0.001
11	STXBPI_6	0.060	<0.001	-0.212	<0.001	-0.474	<0.001	-0.594	<0.001
12	SNAP25_1	0.081	<0.001	-0.279	<0.001	-0.656	<0.001	-0.967	<0.001
13	NDUFA10_2	0.072	<0.001	-0.148	0.01	-0.381	0.026	-0.643	0.001
14	tau_AT100	0.129	<0.001	-0.576	<0.001	-1.364	<0.001	-1.773	<0.001
15	ITPK1_1	0.051	<0.001	-0.133	0.002	NS	NS	-0.504	<0.001
16	SYT7_2	0.057	<0.001	-0.192	<0.001	-0.420	<0.001	-0.542	<0.001
17	NDUFS6_2	0.066	<0.001	-0.203	<0.001	-0.534	<0.001	-0.582	<0.001
18	SNAP25_4	0.064	<0.001	-0.175	<0.001	-0.459	<0.001	-0.646	<0.001
19	UQCRC10_2	0.062	<0.001	0.025	0.04	-0.457	0.013	-0.484	0.017
20	STX1A_2	0.088	<0.001	-0.356	<0.001	-1.013	<0.001	-1.041	<0.001
21	CD47_2	0.095	<0.001	-0.382	<0.001	-1.093	<0.001	-1.258	<0.001
22	NDUFA6_2	0.067	<0.001	-0.187	<0.001	-0.526	0.002	-0.775	<0.001
23	NDUFV1_2	0.055	<0.001	-0.143	<0.01	-0.387	0.009	-0.460	0.005
24	UQCRC2_2	0.061	0.001	-0.193	<0.001	-0.483	0.005	-0.730	<0.001
25	UQCRC2_1	0.067	<0.001	-0.221	<0.001	-0.623	<0.001	-0.994	<0.001
26	VAPB_2	0.114	<0.001	-0.515	<0.001	-1.386	<0.001	-1.475	<0.001
27	NDUFA5_1	0.061	<0.001	-0.117	<0.055	-0.381	0.025	-0.519	0.006
28	SNAP25_3	0.052	<0.001	-0.177	<0.001	-0.511	<0.001	-0.550	<0.001
29	BIN1_4	0.077	<0.001	-0.371	<0.001	-1.073	<0.001	-1.435	<0.001
30	SNAP25_6	0.041	<0.001	-0.169	<0.001	-0.429	<0.001	-0.492	<0.001
31	NDUFV1_1	0.059	<0.001	-0.167	<0.05	-0.447	0.006	-0.490	0.006
32	tau_12E8_s262	-0.026	<0.001	0.105	<0.001	0.224	<0.001	0.445	<0.001
33	IGFBP5_1	-0.050	<0.001	0.133	<0.001	0.324	<0.001	0.457	<0.001
34	tau_AT100_t217	-0.044	<0.001	0.162	<0.001	0.305	<0.001	0.730	<0.001
35	AMPD2_2	-0.093	<0.001	0.263	<0.001	0.558	<0.001	0.991	<0.001
36	GSTP1_1	-0.060	<0.001	0.241	<0.001	0.695	<0.001	0.756	<0.001
37	CLU_2	-0.075	<0.001	0.295	<0.001	0.798	<0.001	0.959	<0.001
38	PTMS_1	-0.062	<0.001	NS	NS	NS	NS	0.474	0.001
39	HSPB2_2	-0.037	<0.001	0.111	<0.001	0.228	0.004	0.447	<0.001
40	C9orf16_2	-0.032	0.001	NS	NS	NS	NS	NS	NS
41	AK4_2	-0.066	<0.001	0.128	<0.05	NS	NS	0.422	0.0412
42	RUVBL1_2	-0.089	<0.001	0.348	<0.001	0.822	<0.001	1.093	<0.001
43	FYN_3	-0.101	<0.001	0.269	<0.001	0.641	0.008	0.768	0.004
44	TPRG1L_1	-0.043	<0.001	NS	NS	NS	NS	NS	NS
45	tau_77G7_s305	-0.019	<0.001	0.077	<0.001	0.135	<0.001	0.348	<0.001
46	AK4_1	-0.073	<0.001	0.168	0.004	0.392	0.024	0.586	0.002
47	SLC6A12_1	-0.034	0.002	0.113	0.002	NS	NS	0.537	<0.001
48	VAMP5_1	-0.024	0.003	0.071	0.008	0.223	0.005	NS	NS
49	VAT1_2	-0.021	0.008	0.096	<0.001	0.346	<0.001	0.340	<0.001
50	SYN2_2	-0.034	0.004	NS	NS	-0.511	<0.001	-0.771	<0.001
51	GRB2_2	-0.099	<0.001	0.340	<0.001	-0.532	<0.001	-0.778	<0.001
52	GFAP_1	-0.027	<0.001	0.128	<0.001	-0.577	<0.001	-0.713	<0.001

Note. Each row is the result of a separate linear mixed-effects model that included terms for demographics only (age before death, sex, and education), and that displays the strength of the association between each protein and annual cognitive decline. The results are ordered by strength of the association (strongest at the top) and by their association with cognitive decline (proteins associated with slower cognitive decline in blue and proteins associated with faster cognitive decline in pink). All p-values were FDR corrected at 5%.

eTable 6. Regression models examining the relation of the cognitive resilience index, with odds of non-AD neuropathology.

	Pathologic Measure (Model Outcome)	Est (S.E., p-Value)
1	Lewy bodies (present)	-.244 (0.065, <0.001)
2	Nigral neuronal loss (moderate-severe)	-.226 (0.080, <0.01)
3	TDP-43 (present beyond amygdala)	-.333 (0.066, <0.001)
4	Hippocampal Sclerosis (present)	-.334 (0.092, <0.001)
5	Macroinfarcts present	-.064 (0.061,0.295)
6	Microinfarcts present	-.081 (0.065,0.211)
7	Atherosclerosis (moderate-severe)	-.073 (0.061,0.238)
8	Arteriolosclerosis (moderate-severe)	-.027 (0.063,0.663)
9	Cerebral amyloid angiopathy (moderate-severe)	-.285 (0.063, <0.001)

Note. Each row is a separate model controlled for age at death, sex, and education. Bolded indicates a significant association.

eTable 7. Logistic models examining the relation of the cognitive resilience index and AD pathology, with odds of diagnosis of dementia, and of mild cognitive impairment proximate to death.

	Model terms	Model 1		Model 2	
A	Dementia proximate to death				
		OR (SE)	<i>p</i> -value	OR (SE)	<i>p</i> -value
	Cognitive resilience index	0.41 (0.08)	<0.001	0.66 (0.13)	<0.01
	Global AD pathology	3.61 (0.11)	<0.001	2.51 (0.12)	<0.001
	Cognitive resilience index X global AD pathology			0.70 (0.14)	0.010
	Cognitive resilience index	0.41 (0.08))	<0.001	0.60 (0.14)	<0.001
	Amyloid	1.64 (0.05)	<0.001	1.39 (0.06)	<0.001
	Cognitive resilience index X amyloid			0.85 (0.07)	0.030
	Cognitive resilience index	0.41 (0.08)	<0.001	0.58 (0.14)	<0.001
	Tau	2.38 (0.07)	<0.001	2.02 (0.08)	<0.001
	Cognitive resilience index X Tau			0.97 (0.08)	0.700
B	MCI proximate to death				
	Cognitive resilience index	0.45 (0.07)	<0.001	0.70 (0.11)	<0.01
	Global AD pathology	3.48 (0.10)	<0.001	2.59 (0.11)	<0.001
	Cognitive resilience index X global AD pathology			0.71 (0.12)	<0.01
	Cognitive resilience index	0.45 (0.07)	<0.001	0.68 (0.12)	<0.01
	Amyloid	1.60 (0.05)	<0.001	1.41(0.05)	<0.001
	Cognitive resilience index X amyloid			0.83 (0.06)	<0.01
	Cognitive resilience index	0.45 (0.07)	<0.001	0.67 (0.12)	<0.001
	Tau	2.40 (0.06)	<0.001	2.05 (0.07)	<0.001
	Cognitive resilience index X Tau			0.93 (0.07)	0.34

Note. Model 1 included separate terms for the cognitive resilience index and each pathologic measure to assess their independent contribution proximate to death. Model 2 included an interaction term to determine whether the cognitive resilience index modified the relation of pathology to a diagnosis of A) dementia and B) mild cognitive impairment, proximate to death. All models were controlled for age at death, sex, and education. AD = Alzheimer's disease. MCI = mild cognitive impairment. OR = odds ratios. SE = standard error.

