Online Resource 1

Supplementary methods, tables and figure

Brain Tissue Proportionality and General Cognitive Ability Across Three Adult Cohorts

Brain Structure and Function | Baptiste Dumoulin

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Supplementary methods

Anatomical variable mapping

HCP-YA. Cortical gray matter = FS_TotCort_GM_Vol; cerebral white matter = FS_Tot_WM_Vol; subcortical gray matter = FS_SubCort_GM_Vol; total cerebellum = FS_L_Cerebellum_Cort_Vol + FS_R_Cerebellum_Cort_Vol + FS_L_Cerebellum_WM_Vol + FS_R_Cerebellum_WM_Vol; brainstem = FS_BrainStem_Vol; eTIV = FS_IntraCranial_Vol.

DLBS Wave 1. Cortical gray matter = CortexVol; cerebral white matter = CortWMVol; subcortical gray matter = SubCortGMVol; total cerebellum = LhCerebellumCortexVol + RhCerebellumCortexVol + LhCerebellumWMVol + RhCerebellumWMVol; brainstem = BrainStemVol; eTIV = TotalIntracranialVol.

AOMIC ID1000. Cortical gray matter = CortexVol; cerebral white matter = CerebralWhiteMatterVol; subcortical gray matter = SubCortGrayVol; total cerebellum = Left-Cerebellum-Cortex + Right-Cerebellum-Cortex + Left-Cerebellum-White-Matter + Right-Cerebellum-White-Matter; brainstem = Brain-Stem; eTIV = EstimatedTotalIntraCranialVol.

The eight source volumes defining the five parts must be positive and finite. The five parts are closed to their sum when proportions are displayed; log-ratio models can use the unclosed volumes because common scaling cancels. The Helmert and rotated five-part bases contain four orthonormal, zero-sum contrasts. Six-part tissue-class and left/right cerebellar models retain all five coordinates. T is the sum of the five modeled tissue compartments, not an exhaustive measure of all intracranial contents.

Cognitive scores and covariates

HCP uses the ten standardized tests in Table S1. DLBS processing speed averages z scores for Digit Comparison and WAIS-III Digit Symbol; working memory averages sign-reversed CANTAB Spatial Working Memory errors with WAIS-III Letter–Number Sequencing; reasoning averages Raven’s and ETS Letter Sets; vocabulary averages ETS Advanced Vocabulary, Shipley Vocabulary and CANTAB Graded Naming; verbal fluency uses the COWA letter total. Baseline subtests are standardized before averaging and the resulting domain composites are standardized before PCA. AOMIC uses its three released IST domains, excluding the redundant total score.

HCP age bands are dummy coded. DLBS age-band midpoint enters patsy bs(age_mid, df=4, degree=3, include_intercept=False), with four spline columns and a separate intercept. AOMIC primary age adjustment is linear. Primary PCA scores and predictor scales are retained for the specified covariate-

complete or influence sensitivity subsets, except the unrelated-HCP sensitivity, whose ILR scales are recomputed as described in Table S7.

Specification and exploratory analyses

AOMIC source: OpenNeuro ds003097 v1.2.1, DOI 10.18112/openneuro.ds003097.v1.2.1, repository commit 47f030747dbaf492acd9f9624528aef8d51d8bd9. Its primary five-part model, total-cerebellum/cerebral-white-matter contrast and original sensitivity models were specified before AOMIC association testing. The original plan and source checksums accompany Supplementary Code 1 (Online Resource 2). This was an internal specification, not a public preregistration. Additional AOMIC analyses in Tables S3–S6 and the two-cohort synthesis in S12 were added after its primary results were known and are exploratory.

The AOMIC primary testing sequence requires a significant global four-coordinate block followed by a positive targeted coefficient assessed with two-sided $\alpha = .05$. Both tests are reported regardless of whether the sequence passes. Exploratory multiplicity families are the ten pairwise balances, the cognitive outcomes within each cohort, and the four cerebellar contrasts within each cohort. Holm adjustment does not correct familial dependence in HCP.

Robust uncertainty, bootstrap and numerical verification

DLBS and AOMIC HC3 tests use residual-degrees-of-freedom t intervals for the focal coefficient and a four-degree-of-freedom Wald F approximation for the global block. Both participant-pairs bootstraps use 2,000 samples of the original sample size drawn with replacement and seed 20261027. PCA weights and orientation, cognitive-score scaling and ILR standardizations are refitted within each resample. DLBS also refits age-spline knots and boundaries, while retaining the defined baseline domain composites; its bootstrap is conditional on the original baseline subtest calibration. All draws succeeded. HCP is not subjected to an individual-participant bootstrap as a substitute for family-aware inference.

Separate numerical implementations verify primary coefficients and HC3 covariance. Rotations of each complete log-ratio basis reproduce identical fitted values. Partial-regression plots remove every other primary regressor, including the remaining three ILRs, from both the standardized focal coordinate and outcome; their slopes reproduce the full-model coefficients. Log(T) + log(eTIV) and log(eTIV) + log(T/eTIV) models give the same fitted values and focal coefficients in each cohort. These checks concern numerical correctness, not independent human review or elimination of confounding.

Two-cohort synthesis

The exploratory synthesis uses DLBS and AOMIC only (N = 1,344). For each uncertainty convention, inverse-variance weights define a fixed-effect average. REML estimates the between-cohort variance for a random-effects average. A normal-approximation interval is accompanied by the modified Knapp–Hartung interval using t with $k-1 = 1$ degree of freedom and a residual-scale multiplier bounded below by one (Röver et al. 2015). Within-cohort standard errors are treated as given in this summary model. Different cognitive batteries and within-cohort SDs limit interpretation of a common standardized effect. Heterogeneity estimates with $k = 2$ are imprecise; the small-k interval is reported alongside the narrow normal interval.

Table S1. PC1 eigenvector weights and AOMIC score correlations

HCP test	PC1 weight	DLBS domain	PC1 weight
Picture Vocabulary	0.384	Processing speed	0.491
Oral Reading	0.404	Working memory	0.501
Matrix Reasoning	0.377	Reasoning	0.521
Spatial Orientation	0.340	Vocabulary	0.179
Picture Sequence Memory	0.261	Verbal fluency	0.452
Card Sort	0.303	—	—
Flanker	0.254	—	—
Processing Speed	0.243	—	—
List Sorting	0.319	—	—
Word Memory	0.216	—	—

AOMIC ID1000

Domain	PC1 eigenvector weight	Correlation with PC1
Fluid intelligence	0.594	0.895
Memory	0.564	0.850
Crystallized intelligence	0.574	0.866

Note. Eigenvector weights multiply standardized inputs; they are distinct from variable–component correlations. Signs were oriented positively. PC1 variance fractions: HCP .33136; DLBS .55063; AOMIC .75790. Percentages differ partly because the number and aggregation of cognitive measures differ.

Table S2. Global composition sensitivity models

Cohort / model	N	Added R^2	Partial R^2	Global OLS p
HCP-YA primary	1,101	0.0368	0.0409	3.01×10^{-9}
HCP-YA eTIV replaces tissue volume	1,101	0.0243	0.0273	4.31×10^{-6}
HCP-YA tissue volume plus eTIV	1,101	0.0323	0.0365	3.25×10^{-8}
HCP-YA one-factor g	1,101	0.0387	0.0432	8.29×10^{-10}
HCP-YA unit-weighted g	1,101	0.0338	0.0372	2.26×10^{-8}
DLBS primary	418	0.0224	0.0420	.00154
DLBS eTIV replaces tissue volume	418	0.0184	0.0329	.00850
DLBS tissue volume plus eTIV	418	0.0221	0.0414	.00176
DLBS one-factor g	418	0.0213	0.0446	.00094
DLBS unit-weighted g	418	0.0288	0.0453	.00082
DLBS categorical age bands	418	0.0241	0.0475	.00081
DLBS plus education	417	0.0192	0.0394	.00261
DLBS MMSE at least 27	386	0.0208	0.0394	.00447
HCP-YA structural QC A/B excluded	1,029	0.0383	0.0427	5.13×10^{-9}
DLBS plus surface defects	418	0.0226	0.0422	.00151
HCP-YA nonlinear allometry	1,101	0.0356	0.0399	5.21×10^{-9}
DLBS nonlinear allometry	418	0.0221	0.0414	.00179

Note. All global tests concern the four ILR coordinates. Full-HCP p values are nominal and do not account for family dependence. Quality exclusion uses public HCP A/B flags; DLBS quality adjustment uses standardized log1p surface-defect count. Nonlinear allometry adds squared centered log tissue volume and sex × centered log tissue volume. All estimates follow the supplied analysis definitions. The unrelated-HCP subset is in S7; the complete AOMIC global sensitivity set is in S8; focal size-adjustment estimates across cohorts are in S10.

Table S3. Raw-volume correlations and conventional comparators

Cohort	Measure	Raw r	Adjusted β	Adjusted p
HCP-YA	Cortical gray matter	0.323	0.359	.00011
HCP-YA	Cerebral white matter	0.233	−0.611	2.55×10^{-10}
HCP-YA	Subcortical gray matter	0.255	−0.043	.470
HCP-YA	Total cerebellum	0.274	0.129	.00342
HCP-YA	Brainstem	0.167	−0.098	.017
HCP-YA	Total analyzed tissue	0.297	—	—
DLBS	Cortical gray matter	0.510	0.186	.053
DLBS	Cerebral white matter	0.205	−0.262	.00563
DLBS	Subcortical gray matter	0.434	−0.014	.841
DLBS	Total cerebellum	0.429	0.168	.00297
DLBS	Brainstem	0.190	−0.006	.913
DLBS	Total analyzed tissue	0.417	—	—
AOMIC	Cortical gray matter	0.256	0.257	.00458
AOMIC	Cerebral white matter	0.204	−0.360	.00023
AOMIC	Subcortical gray matter	0.224	0.031	.649
AOMIC	Total cerebellum	0.196	0.036	.458
AOMIC	Brainstem	0.178	−0.033	.507
AOMIC	Total analyzed tissue	0.246	—	—

Note. Raw r is the Pearson correlation between cognitive PC1 and untransformed volume. Adjusted β comes from a separate model adding one standardized raw compartment volume to age, sex and log total analyzed tissue volume. These are not mutually independent compartment effects. The total-volume row has no analogous adjusted coefficient. P values are conventional; full-HCP values are not family-corrected. All comparators are exploratory.

Table S4. All ten pairwise balances

HCP-YA

Numerator / denominator	β	95% CI	p	Holm p
Total cerebellum / Cerebral white matter	0.204	[0.137, 0.271]	3.68×10^{-9}	3.68×10^{-8}
Cortical gray matter / Cerebral white matter	0.150	[0.085, 0.215]	7.11×10^{-6}	6.40×10^{-5}
Cortical gray matter / Brainstem	0.132	[0.073, 0.192]	1.24×10^{-5}	9.91×10^{-5}
Total cerebellum / Brainstem	0.097	[0.036, 0.158]	.00180	.013
Cerebral white matter / Subcortical gray matter	−0.105	[−0.179, −0.032]	.00514	.031
Cerebral white matter / Brainstem	−0.076	[−0.149, −0.003]	.042	.212
Subcortical gray matter / Brainstem	0.046	[−0.022, 0.114]	.188	.688
Cortical gray matter / Subcortical gray matter	0.045	[−0.020, 0.111]	.172	.688
Subcortical gray matter / Total cerebellum	−0.044	[−0.109, 0.021]	.186	.688
Cortical gray matter / Total cerebellum	0.012	[−0.057, 0.082]	.728	.728

HCP intervals and tests are nominal and not family-corrected.

Note. Each standardized log ratio is rotated to the first coordinate of a complete orthonormal basis; all remaining coordinates and primary covariates are retained. Uncertainty is conventional OLS. Holm adjustment covers the ten contrasts within each cohort. Only the original total-cerebellum/cerebral-white-matter contrast was targeted for DLBS and AOMIC; the other contrasts are exploratory. Pairwise ratios appear in the same orientation across cohorts; reversing a ratio changes the coefficient sign.

Table S4. All ten pairwise balances (continued)

DLBS

Numerator / denominator	β	95% CI	p	Holm p
Total cerebellum / Cerebral white matter	0.162	[0.082, 0.243]	8.79×10^{-5}	.00088
Cortical gray matter / Cerebral white matter	0.104	[0.019, 0.189]	.016	.115
Cortical gray matter / Brainstem	0.065	[−0.016, 0.146]	.117	.702
Total cerebellum / Brainstem	0.101	[0.026, 0.175]	.00843	.076
Cerebral white matter / Subcortical gray matter	−0.041	[−0.130, 0.048]	.369	.914
Cerebral white matter / Brainstem	−0.041	[−0.118, 0.036]	.300	.914
Subcortical gray matter / Brainstem	0.000	[−0.082, 0.082]	.991	.991
Cortical gray matter / Subcortical gray matter	0.045	[−0.028, 0.119]	.228	.914
Subcortical gray matter / Total cerebellum	−0.094	[−0.168, −0.020]	.012	.099
Cortical gray matter / Total cerebellum	−0.055	[−0.132, 0.023]	.166	.828

Note. Each standardized log ratio is rotated to the first coordinate of a complete orthonormal basis; all remaining coordinates and primary covariates are retained. Uncertainty is conventional OLS. Holm adjustment covers the ten contrasts within each cohort. Only the original total-cerebellum/cerebral-white-matter contrast was targeted for DLBS and AOMIC; the other contrasts are exploratory. Pairwise ratios appear in the same orientation across cohorts; reversing a ratio changes the coefficient sign.

Table S4. All ten pairwise balances (continued)

AOMIC

Numerator / denominator	β	95% CI	p	Holm p
Cortical gray matter / Cerebral white matter	0.118	[0.045, 0.191]	.00158	.016
Cortical gray matter / Subcortical gray matter	0.033	[−0.043, 0.109]	.397	1.000
Cortical gray matter / Total cerebellum	0.049	[−0.029, 0.127]	.220	1.000
Cortical gray matter / Brainstem	0.069	[0.002, 0.135]	.043	.346
Cerebral white matter / Subcortical gray matter	−0.073	[−0.158, 0.012]	.091	.547
Total cerebellum / Cerebral white matter	0.097	[0.024, 0.169]	.00906	.082
Cerebral white matter / Brainstem	−0.071	[−0.148, 0.006]	.073	.508
Subcortical gray matter / Total cerebellum	0.001	[−0.073, 0.075]	.979	1.000
Subcortical gray matter / Brainstem	0.012	[−0.069, 0.094]	.766	1.000
Total cerebellum / Brainstem	0.012	[−0.056, 0.079]	.736	1.000

Note. Each standardized log ratio is rotated to the first coordinate of a complete orthonormal basis; all remaining coordinates and primary covariates are retained. Uncertainty is conventional OLS. Holm adjustment covers the ten contrasts within each cohort. Only the original total-cerebellum/cerebral-white-matter contrast was targeted for DLBS and AOMIC; the other contrasts are exploratory. Pairwise ratios appear in the same orientation across cohorts; reversing a ratio changes the coefficient sign.

Table S5. Cognitive-outcome associations with the focal balance

Cohort	Cognitive outcome	β	SE	p	Holm p
HCP-YA	Picture Vocabulary	0.197	0.035	1.79×10^{-8}	1.79×10^{-7}
HCP-YA	Oral Reading	0.155	0.035	1.28×10^{-5}	.00010
HCP-YA	Matrix Reasoning	0.190	0.035	5.38×10^{-8}	4.84×10^{-7}
HCP-YA	Spatial Orientation	0.124	0.035	.00043	.00255
HCP-YA	Picture Sequence Memory	0.082	0.036	.023	.117
HCP-YA	Card Sort	0.062	0.036	.087	.260
HCP-YA	Flanker	0.026	0.036	.469	.469
HCP-YA	Processing Speed	0.056	0.037	.123	.260
HCP-YA	List Sorting	0.136	0.036	.00015	.00103
HCP-YA	Word Memory	0.072	0.037	.050	.202
DLBS	Processing speed	0.088	0.039	.025	.050
DLBS	Working memory	0.117	0.044	.00789	.024
DLBS	Reasoning	0.166	0.043	.00014	.00068
DLBS	Vocabulary	0.200	0.052	.00015	.00068
DLBS	Verbal fluency	0.099	0.052	.056	.056
AOMIC	Fluid intelligence	0.081	0.037	.030	.060
AOMIC	Memory	0.073	0.038	.053	.060
AOMIC	Crystallized intelligence	0.099	0.036	.00689	.021

Note. Standardized outcomes are modeled separately with the primary covariates, focal balance and remaining three ILRs. Conventional OLS standard errors and p values are shown. Holm adjustment is within cohort: ten HCP tests, five DLBS domains, three AOMIC domains. HCP uncertainty is nominal and not family-corrected. AOMIC Holm-adjusted HC3 p values are .0741 for fluid intelligence, .0741 for memory and .0211 for crystallized intelligence. Associations and comparisons are exploratory; differing significance does not demonstrate domain differences.

Table S6. Exploratory cerebellar tissue classes and asymmetry

Cohort	Contrast	β	OLS 95% CI	OLS p / Holm p	HC3 95% CI	HC3 p / Holm p
HCP-YA	Cerebellar cortex / Cerebral white matter	0.219	[0.150, 0.289]	8.21×10^{-10} / 3.28×10^{-9}	—	—
HCP-YA	Cerebellar white matter / Cerebral white matter	0.105	[0.028, 0.182]	.00785 / .016	—	—
HCP-YA	Cerebellar cortex / Cerebellar white matter	0.097	[0.035, 0.159]	.00220 / .00661	—	—
HCP-YA	Left cerebellum / Right cerebellum	0.030	[−0.026, 0.086]	.287 / .287	—	—
DLBS	Cerebellar cortex / Cerebral white matter	0.177	[0.097, 0.258]	1.93×10^{-5} / 7.72×10^{-5}	[0.085, 0.269]	.00017 / .00069
DLBS	Cerebellar white matter / Cerebral white matter	0.066	[−0.018, 0.150]	.125 / .249	[−0.022, 0.154]	.141 / .281
DLBS	Cerebellar cortex / Cerebellar white matter	0.137	[0.052, 0.222]	.00158 / .00475	[0.046, 0.229]	.00345 / .010
DLBS	Left cerebellum / Right cerebellum	−0.012	[−0.083, 0.059]	.735 / .735	[−0.078, 0.054]	.714 / .714
AOMIC	Cerebellar cortex / Cerebral white matter	0.105	[0.031, 0.179]	.00529 / .019	[0.031, 0.179]	.00571 / .023
AOMIC	Cerebellar white matter / Cerebral white matter	0.109	[0.023, 0.195]	.013 / .027	[0.022, 0.196]	.015 / .029
AOMIC	Cerebellar cortex / Cerebellar white matter	0.019	[−0.057, 0.095]	.621 / .621	[−0.058, 0.097]	.628 / .628
AOMIC	Left cerebellum / Right cerebellum	0.090	[0.028, 0.153]	.00469 / .019	[0.025, 0.155]	.00641 / .023

Note. Tissue-class models replace total cerebellum by cortex and white matter. The left/right model instead replaces it by left and right total cerebellum. Each six-part model retains all five ILRs. Each p-value cell gives unadjusted p / Holm-adjusted p across the four contrasts in that cohort. HCP intervals and tests are nominal and not family-corrected; HC3 is therefore not presented as a solution for full HCP. Contrasts are exploratory. Comparing separately standardized coefficient magnitudes is not a formal tissue-class difference test.

Table S7. Official S900 unrelated-HCP sensitivity

Statistic	Estimate
Subjects on the official S900 list	339
Complete cases	337
Added R^2	0.0106
Partial R^2	0.0116
Global conventional p	.432
Global HC3 p	.478
Standardized focal β	0.101
Focal conventional 95% CI	[−0.028, 0.230]
Focal conventional p	.125
Focal HC3 95% CI	[−0.032, 0.234]
Focal HC3 p	.136

Note. The official HCP public S900 list contains 339 unrelated participants selected for T1, T2, complete resting-state fMRI and physiological data; 337 met the primary complete-case definition. Cognitive scores retain the full-HCP PCA and standardization, while ILR scales are recomputed within the subset. Age bands, sex and log total tissue volume remain covariates. This is a nonrandom, internal HCP sensitivity, not an independent replication cohort. The attenuated estimate is retained. The exact public source URL and checksum are provided in Supplementary Code 1 (Online Resource 2) (Human Connectome Project n.d.-b).

Table S8. All original AOMIC global composition models

Model	N	Added R^2	Partial R^2	OLS p	HC3 p
Primary PC1 model	926	0.0126	0.0135	.014	.017
S1 Native IST total	926	0.0119	0.0127	.019	.027
S2 Quadratic age	926	0.0125	0.0134	.014	.017
S3 eTIV replaces tissue scale	926	0.0087	0.0091	.078	.070
S4 Tissue scale plus eTIV	926	0.0127	0.0136	.014	.015
S5 Nonlinear allometry	926	0.0129	0.0138	.012	.015
S6 Surface defect count	926	0.0188	0.0201	.00092	.00166
S7 Education categories	926	0.0152	0.0212	.00060	.00143
S8 Exclude anatomical extremes	925	0.0128	0.0137	.013	.017
S9 Influence diagnostic	878	0.0290	0.0321	1.02×10^{-5}	3.75×10^{-6}

Note. The primary model includes age, sex and log total tissue volume plus four ILRs. OLS p values use the four-df nested-model F test; HC3 values use the four-df Wald F approximation. The complete original sensitivity set is reported. S3 replaces tissue volume by eTIV; S4 includes both. Nonlinear allometry adds squared centered log tissue volume and sex × centered log tissue volume. The complete-case primary sample remains unchanged.

Table S9. All original AOMIC targeted-balance models

Model	β	OLS 95% CI	OLS p	HC3 95% CI	HC3 p
Primary PC1 model	0.097	[0.024, 0.169]	.00906	[0.024, 0.170]	.00965
S1 Native IST total	0.093	[0.021, 0.166]	.012	[0.019, 0.168]	.014
S2 Quadratic age	0.096	[0.023, 0.169]	.00964	[0.023, 0.170]	.010
S3 eTIV replaces tissue scale	0.017	[−0.051, 0.084]	.631	[−0.055, 0.088]	.648
S4 Tissue scale plus eTIV	0.098	[0.025, 0.172]	.00884	[0.026, 0.171]	.00807
S5 Nonlinear allometry	0.098	[0.025, 0.170]	.00847	[0.024, 0.171]	.00916
S6 Surface defect count	0.126	[0.051, 0.202]	.00109	[0.050, 0.203]	.00122
S7 Education categories	0.114	[0.051, 0.178]	.00045	[0.047, 0.182]	.00096
S8 Exclude anatomical extremes	0.097	[0.024, 0.170]	.00886	[0.024, 0.170]	.00949
S9 Influence diagnostic	0.113	[0.047, 0.179]	.00080	[0.049, 0.178]	.00060

Note. β is the standardized coefficient for the original total-cerebellum/cerebral-white-matter balance, with the three remaining coordinates retained. Intervals are t based. PCA weights and predictor scales are retained for subset models. S8 removes one preidentified anatomical extreme; S9 removes 48 observations with Cook’s distance > 4/N and is an influence diagnostic, not a revised primary sample. The eTIV-only attenuation remains reported.

Table S10. Focal coefficients under alternative size adjustment

Cohort	Scale covariates	β	OLS 95% CI	OLS p	HC3 95% CI	HC3 p
HCP-YA	Tissue	0.204	[0.137, 0.271]	3.68×10^{-9}	—	—
HCP-YA	eTIV only	0.125	[0.063, 0.186]	7.64×10^{-5}	—	—
HCP-YA	Both	0.186	[0.118, 0.253]	9.08×10^{-8}	—	—
DLBS	Tissue	0.162	[0.082, 0.243]	8.79×10^{-5}	[0.072, 0.252]	.00043
DLBS	eTIV only	0.108	[0.029, 0.187]	.00782	[0.026, 0.190]	.010
DLBS	Both	0.163	[0.083, 0.244]	7.98×10^{-5}	[0.072, 0.254]	.00047
AOMIC	Tissue	0.097	[0.024, 0.169]	.00906	[0.024, 0.170]	.00965
AOMIC	eTIV only	0.017	[−0.051, 0.084]	.631	[−0.055, 0.088]	.648
AOMIC	Both	0.098	[0.025, 0.172]	.00884	[0.026, 0.171]	.00807

Note. T is the sum of the five analyzed compartments. Tissue uses log(T); eTIV only replaces log(T) with log(eTIV); Both includes both covariates. Every model retains the same age, sex and complete four-coordinate composition adjustment. HCP uncertainty is nominal and not family-corrected. Model replacement changes the conditional association being estimated. Including both size covariates is exactly equivalent to including log(eTIV) and log(T/eTIV). T/eTIV is a selected-tissue ratio, not an exhaustive parenchymal fraction. Algebraic equivalence is not evidence for a causal explanation of attenuation.

Table S11. Uncertainty checks in both confirmation cohorts

Cohort	Method	N	β	SE / bootstrap SD	95% interval	p
DLBS	OLS	418	0.162	0.041	[0.082, 0.243]	8.79×10^{-5}
DLBS	HC3	418	0.162	0.046	[0.072, 0.252]	.00043
DLBS	Pairs bootstrap	418	0.162	0.048	[0.067, 0.256]	—
AOMIC	OLS	926	0.097	0.037	[0.024, 0.169]	.00906
AOMIC	HC3	926	0.097	0.037	[0.024, 0.170]	.00965
AOMIC	Pairs bootstrap	926	0.097	0.036	[0.025, 0.165]	—

Note. OLS and HC3 intervals use t quantiles; bootstrap intervals are percentile intervals from 2,000 successful participant-pairs draws per cohort. The displayed β remains the original point estimate. Bootstrap SD describes the distribution of refitted coefficients and is not used here to derive a p value. PCA and standardizations are refitted per draw; DLBS also refits its spline, conditional on the original baseline domain-composite definitions. This common resampling framework does not imply identical cognitive measurement across cohorts.

Table S12. Exploratory DLBS–AOMIC synthesis

Within-cohort SE	Summary method	β	95% CI	p
OLS	Fixed effect	0.126	[0.072, 0.180]	4.29×10^{-6}
OLS	REML, normal approximation	0.127	[0.063, 0.191]	9.58×10^{-5}
OLS	REML, modified Knapp–Hartung	0.127	[−0.287, 0.541]	.160
HC3	Fixed effect	0.123	[0.066, 0.180]	2.09×10^{-5}
HC3	REML, normal approximation	0.124	[0.061, 0.187]	.00012
HC3	REML, modified Knapp–Hartung	0.124	[−0.286, 0.534]	.162

Note. Two cohorts (N = 1,344); full HCP is excluded. This synthesis was added after the cohort-specific results were known. HC3 is the principal within-cohort uncertainty convention; OLS is a sensitivity. Heterogeneity: OLS Q = 1.402, I^2 = 28.7%, REML τ^2 = .000613; HC3 Q = 1.227, I^2 = 18.5%, REML τ^2 = .000396. These estimates are poorly determined with k = 2. The modified Knapp–Hartung interval uses one degree of freedom (97.5th-percentile t = 12.71 versus normal z = 1.96) and a variance multiplier bounded below by one; its interval includes zero. Different cognitive batteries, age adjustments and within-cohort SDs limit interpretation as a common biological effect. The wide small-k interval must be considered alongside the narrow normal-approximation interval; neither replaces the cohort-specific analyses.

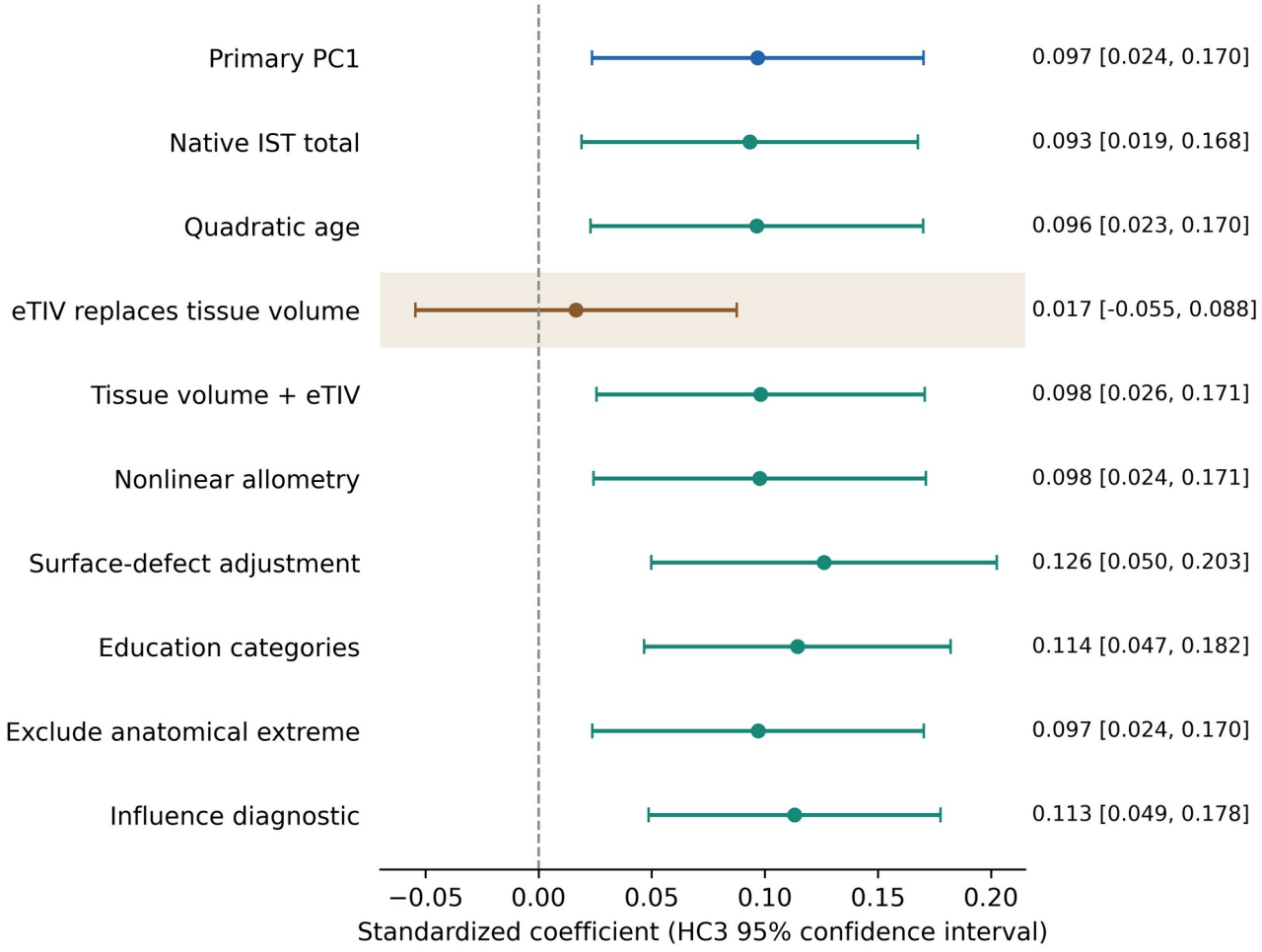


Fig. S1 AOMIC targeted-balance sensitivities. Points and horizontal lines show standardized coefficients and HC3 95% confidence intervals for the primary model and every original sensitivity model. The eTIV-replacement model is highlighted to show its distinct adjustment target and attenuated association. Native IST total is a secondary cognitive outcome. Anatomical-extreme exclusion retained N = 925; the influence diagnostic retained N = 878. Influence exclusions are diagnostic only. No sensitivity result replaces the complete-sample primary estimate.

References for Online Resource 1

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