Supplementary Material

Supplementary Materials and Methods

Table S1 Demographics

	PNC (N=1,347)		HCP (N=1,032)		OASIS-3 (N=609)	
	male	female	male	female	male	female
n	615	732	507	606	240	369
Age, mean (SD)*	14.14 (3.48)	14.61 (3.50)	27.90 (3.61)	29.56 (3.60)	68.51 (8.97)	66.54 (9.10)
Age, range	8-21	8-21	22-36	22-37	42-89	43-95

*****There were significant age differences between males and females in each cohort. HCP - Human Connectome Project, OASIS-3 - Open Access Series of Imaging Studies, PNC - Philadelphia Neurodevelopmental Cohort, SD - standard deviation.

Data acquisition

Child and Youth - PNC

Data for participants (n=1,601, aged 8-23) were included from the publicly available PNC dataset [1]. Participants were scanned on the same 3T Siemens TIM Trio scanner at the Hospital of the University of Pennsylvania. T1-weighted images were acquired with a magnetization prepared, rapid-acquisition gradient-echo (MPRAGE) sequence with the following parameters: TR=1810 ms, TE=3.5 ms, TI=1100 ms, 9° flip angle and matrix of 192 x 256, resulting in a resolution of 0.94 x 0.94 x 1 mm^3. Subjects were excluded based on missing data/processing errors (n=122), quality control (see Quality Control section below, n=51) and the presence of a major medical condition (n=81; e.g. epilepsy, skull fracture, meningitis, multiple sclerosis) resulting in n=1,347 individuals for analysis.

Young Adult - HCP

The HCP Young Adult S1200 (age 22-37) data were used [2]. Only broadly healthy individuals were recruited to participate. T1-weighted data were collected on a custom 3T Siemens Skyra with a 3D MPRAGE sequence with the following parameters: TR=2400 ms, TE=2.14 ms, TI=1000, 8° flip angle and matrix of 320 x 256, resulting in a 0.7 mm^3 isotropic resolution [2]. High quality processed data were available for n=1,113 subjects.

Late-Life - OASIS-3

All MRI data included in this analysis were collected on one of two Siemens TIM Trio 3T MRI scanners at the Knight Alzheimer's Disease Research Center, Washington University in St

Louis with the following T1-weighted parameters: TR=400 ms, TE=3.16 ms, TI=1000 ms, 8° flip angle and matrix of 256 x 256, resulting in a 1 mm^3 isotropic resolution.

Quality Control (QC)

PNC FreeSurfer outputs were visually inspected in-house to ensure image quality and accurate segmentation of the grey and white matter. HCP data were quality controlled before being released. Similarly, the OASIS-3 FreeSurfer data were visually checked before release [3] - only data that passed inspection were included.

Data and Code Availability

All data used in this study are publicly available from their respective sources. For details see related publications; PNC [1], HCP [2] and OASIS-3 [4–6]. All custom code used for this study are freely available at https://github.com/nat-tigr/numerical_algorithms.

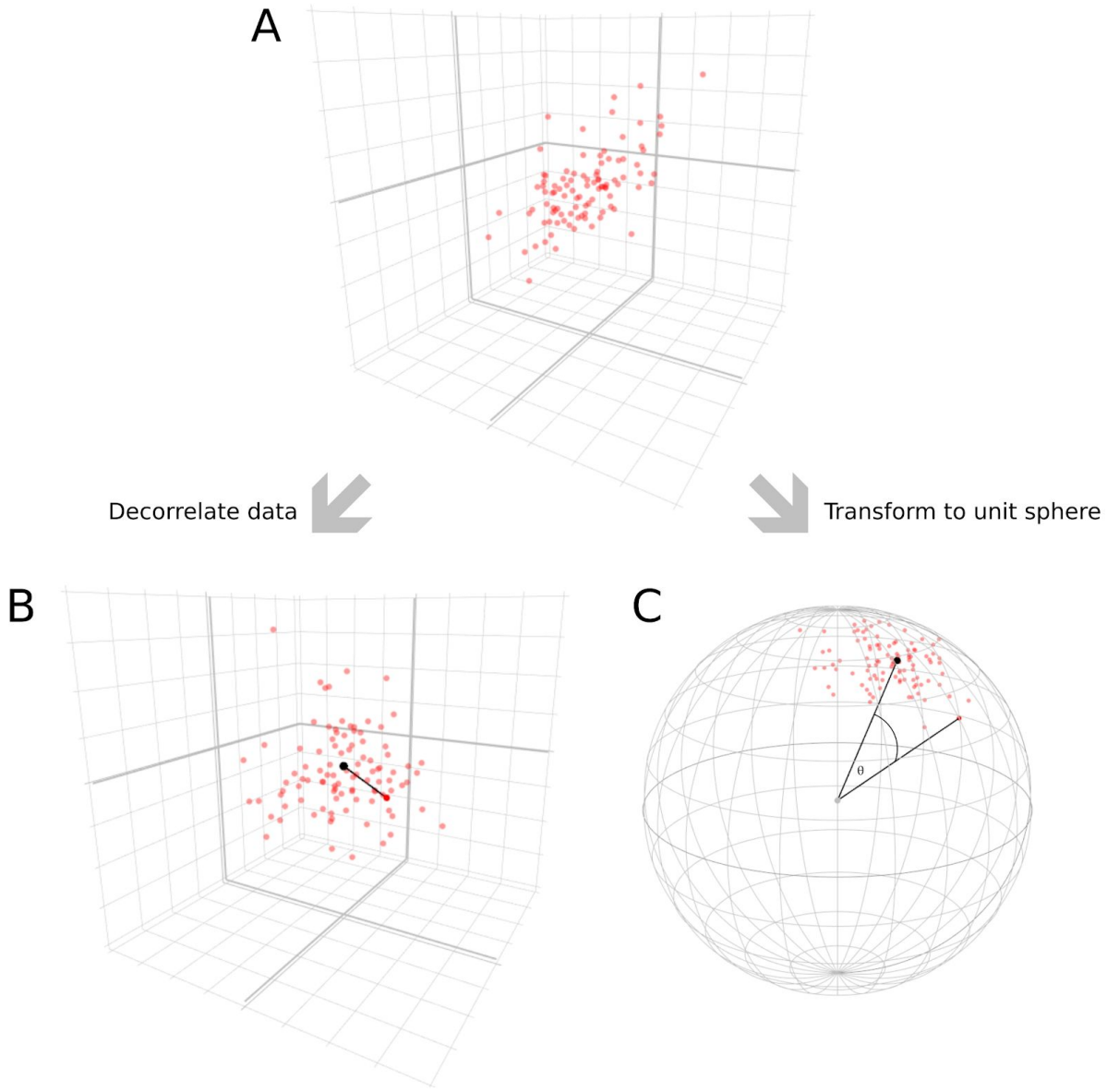

Figure S1 Simplified 3-dimensional schematic of the analytic methods
Each red point represents a subject per figure. (A) Raw data showing correlation between measures. (B) Displays data that has undergone a whitening or decorrelation step that occurs as part of Mahalanobis distance calculation. On decorrelated data the Mahalanobis distance is equivalent to the Euclidean distance between points. Distance (e.g. black line) is calculated between each subject (red point) and the data mean (black point) to give a multivariate measure of deviation based on distribution (or variance). (C) Shows data that has been normalised to the unit sphere. The magnitude of the measures are thus no longer represented but the proximity of points on the surface of the sphere indicates the correlational similarity of the subjects across all measures. The dissimilarity was quantified by calculating the cosine angle (θ) between each subject (red points) and the data centroid (black point). Black lines show an example.

Supplementary Results

Variance Ratios

Full results from main manuscript

Table S2 Variance in Volumes

			PNC		HCP		OASIS-3	
			VR	q	VR	q	VR	q
Global Volumes								
TBV		raw	1.20	0.09	1.36	**0.002**	1.38	**0.001**
Cerebral GM		raw	1.18	0.09	1.31	**0.003**	1.32	**0.003**
		corrected	1.22	**0.02**	1.36	**8.4E-04**	1.41	**2.5E-04**
Cerebral WM		raw	1.25	**0.02**	1.42	**9.7E-05**	1.45	**1.4E-04**
		corrected	1.25	**0.02**	1.32	**0.002**	1.37	**6.8E-04**
Cerebellar GM		raw	1.13	0.19	1.15	0.13	1.07	0.54
		corrected	1.20	**0.03**	1.14	0.15	1.10	0.36
Cerebellar WM		raw	0.97	0.89	1.49	**1.4E-05**	1.39	**4.6E-04**
		corrected	0.99	1	1.64	**2.4E-08**	1.58	**1.1E-06**
Subcortical Volumes								
Thalamus	left	raw	1.14	0.15	1.27	**0.01**	1.22	0.09
		corrected	1.41	**1.3E-04**	1.17	0.09	1.09	0.44
	right	raw	1.28	**0.02**	1.35	**0.002**	1.84	**9.4E-07**
		corrected	1.32	**0.003**	1.26	**0.03**	1.52	**8.6E-04**
Caudate	left	raw	1.26	**0.02**	1.25	**0.02**	1.69	**2.5E-05**
		corrected	1.25	**0.01**	1.11	0.30	1.64	**1.4E-04**
	right	raw	1.18	0.07	1.31	**0.005**	1.58	**2.2E-04**
		corrected	1.17	0.07	1.20	0.07	1.53	**8.1E-04**
Putamen	left	raw	1.20	0.05	1.09	0.34	1.59	**2.2E-04**
		corrected	1.14	0.14	1.09	0.38	1.59	**3.2E-04**
	right	raw	1.21	0.05	1.16	0.11	1.86	**9.4E-07**
		corrected	1.21	**0.02**	1.11	0.30	1.74	**2.3E-05**
Pallidum	left	raw	1.18	0.07	1.05	0.60	1.36	**0.01**
		corrected	1.26	**0.01**	0.99	0.89	1.33	**0.03**
	right	raw	1.20	0.05	1.09	0.34	1.35	**0.01**
		corrected	1.25	**0.01**	1.06	0.56	1.24	0.07
Hippocampus	left	raw	0.98	0.80	1.55	**3.9E-06**	1.37	**0.009**
		corrected	0.96	0.66	1.68	**1.5E-08**	1.25	0.06
	right	raw	1.03	0.78	1.17	0.10	1.53	**5.1E-04**
		corrected	1.03	0.66	1.22	0.05	1.41	**0.008**
Amygdala	left	raw	1.11	0.27	1.39	**7.0E-04**	1.56	**2.7E-04**
		corrected	1.23	**0.02**	1.31	**0.01**	1.30	**0.04**
	right	raw	1.12	0.21	1.24	**0.02**	1.44	**0.003**
		corrected	1.19	0.05	1.17	0.09	1.32	**0.03**
Nucleus Accumbens	left	raw	1.10	0.29	1.24	**0.02**	1.27	**0.04**
		corrected	1.12	0.17	1.24	**0.04**	1.26	0.06
	right	raw	1.07	0.48	1.25	**0.02**	1.41	**0.004**
		corrected	1.07	0.45	1.17	0.09	1.36	**0.02**

Results from analyses of sex differences for gloabl and subcortical brain volumes are presented from the Philadelphia Neurodevelopmental Cohort (PNC), Human Connectome Project (HCP) and Open Access Series of Imaging Studies (OASIS-3). Variance ratios (VR) were calculated from F-tests, VR>1 indicates males > females and VR<1 indicates females > males in variance. 'Raw' results represent findings from volumes corrected for age (age

effects regressed out). Corresponding 'corrected' results were generated from volumes corrected for total brain volume (TBV) as well as age. GM - grey matter, WM - white matter, *q* - False Discovery Rate (FDR) corrected *p*-value.

Table S3 Variance in Surface Area

		PNC				HCP				OASIS			
		RAW		CORRECTED		RAW		CORRECTED		RAW		CORRECTED	
		VR	q	VR	q	VR	q	VR	q	VR	q	VR	q
Bankssts	left	1.44	2.5E-05	1.53	3.4E-07	1.67	2.3E-08	1.62	1.0E-07	1.51	2.5E-03	1.61	3.8E-04
	right	1.43	2.5E-05	1.59	3.4E-08	1.41	1.6E-04	1.33	1.4E-03	1.19	0.17	1.35	0.03
Caudalanterior-cingulate	left	1.24	9.3E-03	1.37	1.7E-04	1.24	0.01	1.30	3.7E-03	1.37	0.02	1.21	0.16
	right	1.23	0.01	1.28	2.8E-03	1.21	0.03	1.15	0.12	1.16	0.25	1.17	0.24
Caudalmiddle-frontal	left	1.15	0.08	1.24	9.7E-03	1.47	3.5E-05	1.56	1.1E-06	1.43	7.6E-03	1.26	0.09
	right	1.19	0.03	1.26	4.8E-03	1.49	1.9E-05	1.53	4.2E-06	1.54	1.6E-03	1.51	2.2E-03
Cuneus	left	1.29	2.3E-03	1.26	4.9E-03	0.97	0.77	1.14	0.13	1.19	0.17	1.24	0.12
	right	1.22	0.02	1.20	0.03	0.98	0.82	1.11	0.24	1.13	0.32	1.04	0.82
Entorhinal	left	1.24	9.3E-03	1.27	4.7E-03	2.14	0	2.15	0	1.22	0.12	1.20	0.16
	right	1.27	4.5E-03	1.34	4.7E-04	1.78	3.8E-10	1.69	1.4E-08	1.65	1.9E-04	1.73	7.7E-05
Frontalpole	left	1.19	0.03	1.14	0.11	1.24	0.02	1.15	0.11	1.33	0.03	1.27	0.08
	right	1.40	9.1E-05	1.35	3.3E-04	1.12	0.20	0.95	0.58	1.38	0.01	1.27	0.08
Fusiform	left	1.07	0.38	1.23	0.01	1.28	6.7E-03	1.42	9.1E-05	1.32	0.03	1.50	2.2E-03
	right	1.22	0.02	1.25	5.8E-03	1.31	2.7E-03	1.27	7.1E-03	1.21	0.14	0.98	0.86
Inferior-parietal	left	1.17	0.05	1.49	1.8E-06	1.25	0.01	1.33	1.3E-03	1.46	4.6E-03	1.57	8.0E-04
	right	1.43	2.5E-05	1.59	3.4E-08	1.37	5.4E-04	1.47	2.6E-05	1.65	1.9E-04	1.66	1.7E-04
Inferior-temporal	left	1.22	0.02	1.26	4.8E-03	1.33	1.3E-03	1.27	7.8E-03	1.34	0.02	1.13	0.33
	right	1.15	0.09	1.26	5.3E-03	1.43	9.6E-05	1.50	1.0E-05	1.34	0.02	1.15	0.30
Insula	left	1.44	2.5E-05	1.59	3.4E-08	1.37	4.7E-04	1.37	4.3E-04	1.17	0.21	1.23	0.12
	right	1.38	1.7E-04	1.38	1.2E-04	1.12	0.18	1.07	0.44	1.32	0.03	1.40	0.01
Isthmus-cingulate	left	1.43	2.5E-05	1.38	1.5E-04	1.50	1.8E-05	1.50	9.5E-06	1.06	0.61	1.04	0.81
	right	1.34	6.6E-04	1.46	7.3E-06	1.75	1.3E-09	1.75	1.1E-09	1.32	0.03	1.17	0.24
Lateral-occipital	left	1.31	1.5E-03	1.16	0.06	1.24	0.01	1.38	3.4E-04	1.12	0.35	1.16	0.26
	right	1.34	5.2E-04	1.25	6.4E-03	1.19	0.05	1.33	1.4E-03	1.33	0.03	1.30	0.05
Lateral-orbitofrontal	left	1.08	0.33	1.09	0.28	1.16	0.09	1.11	0.25	1.14	0.31	0.98	0.86
	right	1.14	0.10	1.16	0.07	1.27	7.8E-03	1.16	0.09	1.16	0.25	1.03	0.86
Lingual	left	1.10	0.24	1.05	0.57	1.20	0.04	1.29	4.1E-03	1.33	0.03	1.17	0.24
	right	1.11	0.19	1.00	0.99	1.38	4.1E-04	1.63	9.0E-08	1.28	0.05	1.10	0.45
Medial-orbitofrontal	left	1.35	5.0E-04	1.39	9.1E-05	1.24	0.01	1.32	1.7E-03	1.08	0.54	1.04	0.82
	right	1.23	0.01	1.19	0.03	1.31	2.9E-03	1.20	0.05	1.30	0.04	1.21	0.16
Middle-temporal	left	1.37	2.9E-04	1.34	4.2E-04	1.25	0.01	1.26	0.01	1.47	4.4E-03	1.31	0.05
	right	1.21	0.02	1.35	2.8E-04	1.09	0.30	1.19	0.05	1.39	0.01	1.38	0.02
Paracentral	left	1.30	2.2E-03	1.31	1.2E-03	1.53	5.8E-06	1.44	6.7E-05	1.24	0.09	1.25	0.09
	right	1.30	2.2E-03	1.33	5.9E-04	1.37	5.4E-04	1.38	4.0E-04	1.45	5.3E-03	1.48	3.0E-03
Para-hippocampal	left	1.34	5.2E-04	1.40	7.1E-05	1.42	1.5E-04	1.39	2.9E-04	1.41	0.01	1.34	0.03
	right	1.56	5.3E-07	1.57	7.9E-08	1.36	6.8E-04	1.39	2.9E-04	1.49	3.1E-03	1.28	0.07
Pars-opercularis	left	1.35	5.2E-04	1.37	2.0E-04	1.36	6.8E-04	1.34	1.2E-03	1.56	1.3E-03	1.64	2.5E-04
	right	1.23	0.01	1.35	3.3E-04	1.48	2.9E-05	1.46	3.1E-05	1.36	0.02	1.47	3.6E-03
Parsorbitalis	left	1.08	0.33	1.12	0.18	1.20	0.04	1.15	0.12	1.13	0.33	1.23	0.13
	right	1.29	2.4E-03	1.22	0.02	1.27	7.8E-03	1.19	0.05	1.01	0.91	1.03	0.85
Pars-triangularis	left	1.26	5.2E-03	1.28	3.1E-03	1.37	4.7E-04	1.27	7.4E-03	1.27	0.06	1.43	6.7E-03
	right	1.37	2.2E-04	1.40	8.2E-05	1.38	3.9E-04	1.42	9.1E-05	1.38	0.01	1.46	4.1E-03
Pericalcarine	left	1.05	0.54	0.97	0.71	1.08	0.38	1.11	0.25	1.07	0.58	0.97	0.85

	right	1.18	0.04	1.07	0.39	0.97	0.75	1.03	0.69	0.96	0.78	0.85	0.24
Postcentral	left	1.27	4.5E-03	1.30	1.6E-03	1.49	1.9E-05	1.68	1.8E-08	1.41	0.01	1.30	0.05
	right	1.24	0.01	1.19	0.03	1.30	2.9E-03	1.35	9.7E-04	1.53	1.6E-03	1.61	3.8E-04
Posterior-cingulate	left	1.12	0.17	1.12	0.17	1.53	5.8E-06	1.65	5.1E-08	2.40	2.4E-12	2.80	0
	right	1.31	1.6E-03	1.36	2.2E-04	1.38	4.1E-04	1.33	1.5E-03	1.30	0.04	1.15	0.30
Precentral	left	1.28	2.9E-03	1.22	0.01	1.55	3.5E-06	1.78	4.9E-10	1.68	1.3E-04	1.54	1.5E-03
	right	1.19	0.04	1.09	0.29	1.27	7.9E-03	1.30	3.1E-03	1.69	1.3E-04	1.68	1.7E-04
Precuneus	left	1.29	2.8E-03	1.26	5.5E-03	1.32	2.1E-03	1.19	0.05	1.39	0.01	1.35	0.03
	right	1.26	5.2E-03	1.32	8.2E-04	1.36	5.9E-04	1.22	0.03	1.75	4.5E-05	1.67	1.7E-04
Rostralanterior-cingulate	left	1.01	0.86	1.06	0.51	1.23	0.02	1.23	0.02	1.39	0.01	1.22	0.14
	right	1.12	0.16	1.14	0.11	1.34	1.0E-03	1.44	6.3E-05	1.24	0.09	1.11	0.41
Rostral-middlefrontal	left	1.46	1.7E-05	1.48	3.6E-06	1.47	3.4E-05	1.49	1.1E-05	1.36	0.02	1.50	2.2E-03
	right	1.31	1.4E-03	1.20	0.02	1.33	1.6E-03	1.43	6.9E-05	1.40	0.01	1.46	3.9E-03
Superior-frontal	left	1.26	5.6E-03	1.21	0.02	1.45	5.0E-05	1.45	4.4E-05	1.38	0.02	1.22	0.13
	right	1.27	4.6E-03	1.26	5.7E-03	1.38	4.1E-04	1.23	0.02	1.40	0.01	1.33	0.04
Superior-parietal	left	1.27	3.8E-03	1.32	8.6E-04	1.28	6.7E-03	1.35	9.1E-04	1.37	0.02	1.14	0.33
	right	1.17	0.05	1.06	0.45	1.22	0.02	1.21	0.03	1.17	0.22	1.00	0.97
Superior-temporal	left	1.19	0.03	1.21	0.02	1.38	4.1E-04	1.56	1.3E-06	1.37	0.02	1.30	0.05
	right	1.08	0.33	1.10	0.23	1.45	5.0E-05	1.33	1.5E-03	1.08	0.52	1.18	0.21
Supramarginal	left	1.47	1.7E-05	1.43	2.1E-05	1.38	3.9E-04	1.41	1.2E-04	1.21	0.13	1.30	0.05
	right	1.30	2.1E-03	1.60	3.4E-08	1.39	3.9E-04	1.50	9.5E-06	1.29	0.04	1.18	0.21
Temporalpole	left	1.30	1.9E-03	1.36	2.4E-04	1.22	0.02	1.22	0.02	1.50	2.8E-03	1.51	2.2E-03
	right	1.46	1.7E-05	1.56	1.1E-07	1.16	0.09	1.16	0.10	1.27	0.06	1.32	0.04
Transverse-temporal	left	1.17	0.06	1.17	0.05	1.43	9.6E-05	1.49	1.0E-05	1.31	0.03	1.30	0.05
	right	1.06	0.45	1.00	0.97	1.46	4.3E-05	1.37	4.5E-04	1.53	1.6E-03	1.48	3.4E-03

Table S4 Variance in Cortical Thickness

		PNC				HCP				OASIS			
		RAW		CORRECTED		RAW		CORRECTED		RAW		CORRECTED	
		VR	q	VR	q	VR	q	VR	q	VR	q	VR	q
Bankssts	left	0.99	1.00	1.00	0.98	1.14	0.34	1.15	0.30	1.11	0.78	1.11	0.84
	right	1.12	0.69	1.13	0.64	1.27	0.07	1.26	0.07	1.17	0.65	1.17	0.75
Caudalanterior-cingulate	left	0.77	0.05	0.78	0.09	1.02	0.97	1.02	0.97	1.02	0.95	1.06	0.96
	right	0.78	0.05	0.79	0.09	0.95	0.82	0.94	0.79	0.98	0.95	1.02	1.00
Caudalmiddle-frontal	left	1.05	0.99	1.05	0.96	1.01	0.97	1.02	0.97	1.01	0.95	1.00	1.00
	right	0.99	1.00	0.99	0.98	1.00	0.99	0.99	0.97	1.01	0.95	1.01	1.00
Cuneus	left	1.01	1.00	1.01	0.98	1.06	0.82	1.05	0.85	1.07	0.95	1.06	0.96
	right	0.97	0.99	0.96	0.96	1.02	0.97	1.01	0.97	0.98	0.95	0.98	1.00
Entorhinal	left	0.97	0.99	0.96	0.96	1.27	0.07	1.27	0.07	1.19	0.65	1.18	0.73
	right	1.11	0.70	1.11	0.75	1.13	0.37	1.14	0.31	1.14	0.77	1.14	0.78
Frontalpole	left	1.12	0.69	1.13	0.64	1.01	0.97	1.02	0.97	0.84	0.65	0.87	0.78
	right	1.00	1.00	0.99	0.98	0.96	0.86	0.96	0.87	0.86	0.68	0.89	0.84
Fusiform	left	1.02	0.99	1.04	0.96	1.06	0.81	1.07	0.70	0.99	0.95	1.00	1.00
	right	0.98	0.99	0.97	0.97	1.05	0.82	1.08	0.67	1.06	0.95	1.06	0.99
Inferior-parietal	left	0.99	1.00	0.98	0.98	1.22	0.12	1.22	0.11	1.03	0.95	1.03	1.00
	right	1.03	0.99	1.03	0.97	1.10	0.56	1.10	0.55	1.11	0.78	1.11	0.85
Inferior-temporal	left	0.97	0.99	0.98	0.98	1.28	0.07	1.28	0.07	0.96	0.95	0.98	1.00
	right	1.06	0.99	1.06	0.96	1.26	0.07	1.26	0.07	1.05	0.95	1.05	0.99
Insula	left	1.16	0.69	1.17	0.63	1.00	0.99	0.99	0.97	1.10	0.80	1.08	0.92
	right	1.09	0.82	1.10	0.77	0.91	0.54	0.88	0.37	1.26	0.60	1.27	0.52
Isthmus-cingulate	left	1.17	0.68	1.17	0.63	1.44	0.001	1.44	0.001	0.94	0.95	0.96	1.00
	right	1.04	0.99	1.04	0.96	1.14	0.34	1.14	0.31	0.85	0.65	0.85	0.75
Lateral-occipital	left	1.00	1.00	1.00	0.98	1.17	0.28	1.16	0.28	0.96	0.95	0.92	0.92
	right	0.89	0.69	0.88	0.64	1.25	0.08	1.28	0.07	1.06	0.95	1.01	1.00
Lateral-orbitofrontal	left	0.95	0.99	0.95	0.96	1.15	0.32	1.17	0.28	1.24	0.64	1.26	0.56
	right	1.05	0.99	1.05	0.96	1.03	0.94	1.02	0.97	0.85	0.65	0.89	0.84
Lingual	left	1.00	1.00	1.00	0.98	1.10	0.56	1.08	0.67	1.07	0.94	1.05	0.99
	right	0.90	0.70	0.91	0.77	1.13	0.40	1.13	0.35	1.12	0.78	1.07	0.96
Medial-orbitofrontal	left	1.10	0.71	1.10	0.77	1.00	0.99	1.00	0.97	1.07	0.94	1.09	0.92
	right	1.02	1.00	1.01	0.98	1.00	0.99	1.00	0.97	1.03	0.95	1.10	0.87
Middle-temporal	left	1.14	0.69	1.15	0.63	1.04	0.86	1.05	0.85	1.12	0.78	1.11	0.84
	right	1.03	0.99	1.03	0.97	1.21	0.12	1.21	0.11	1.32	0.42	1.32	0.37
Paracentral	left	0.95	0.99	0.93	0.90	1.08	0.68	1.08	0.67	1.01	0.95	1.00	1.00
	right	1.02	1.00	1.03	0.96	1.06	0.80	1.06	0.75	0.98	0.95	0.97	1.00
Para-hippocampal	left	0.98	1.00	0.98	0.98	1.03	0.93	1.04	0.88	1.16	0.65	1.18	0.73
	right	0.93	0.98	0.93	0.90	0.99	0.99	0.99	0.97	1.30	0.43	1.30	0.40
Pars-opercularis	left	1.06	0.99	1.07	0.90	1.32	0.04	1.33	0.03	1.11	0.78	1.11	0.84
	right	0.97	0.99	0.97	0.97	1.06	0.82	1.07	0.70	1.02	0.95	1.00	1.00
Parsorbitalis	left	1.03	0.99	1.03	0.96	0.90	0.54	0.90	0.51	0.95	0.95	0.95	0.99
	right	1.11	0.70	1.11	0.77	0.93	0.72	0.93	0.70	0.84	0.65	0.83	0.73
Pars-triangularis	left	1.04	0.99	1.04	0.96	1.08	0.71	1.08	0.67	1.03	0.95	1.04	1.00
	right	0.96	0.99	0.96	0.96	0.97	0.93	0.96	0.87	0.99	0.95	0.98	1.00
Pericalcarine	left	1.13	0.69	1.12	0.64	0.99	0.99	0.99	0.97	0.89	0.78	0.89	0.84

	right	0.96	0.99	0.95	0.96	0.99	0.99	1.01	0.97	1.03	0.95	1.01	1.00
Postcentral	left	0.90	0.70	0.86	0.63	1.05	0.82	1.04	0.87	1.01	0.95	1.00	1.00
	right	1.15	0.69	1.12	0.65	1.05	0.82	1.05	0.85	0.98	0.95	0.96	0.99
Posterior-cingulate	left	0.96	0.99	0.96	0.96	1.22	0.12	1.21	0.11	1.59	0.004	1.60	0.003
	right	0.96	0.99	0.96	0.96	1.14	0.34	1.14	0.31	0.91	0.82	0.91	0.88
Precentral	left	1.01	1.00	1.01	0.98	1.20	0.14	1.22	0.11	1.05	0.95	1.03	1.00
	right	0.93	0.99	0.93	0.90	1.21	0.12	1.23	0.10	1.03	0.95	1.01	1.00
Precuneus	left	1.00	1.00	1.01	0.98	1.10	0.54	1.12	0.44	1.14	0.77	1.10	0.87
	right	0.93	0.98	0.92	0.90	1.16	0.28	1.16	0.28	1.25	0.62	1.20	0.73
Rostralanterior-cingulate	left	0.88	0.69	0.88	0.64	0.98	0.97	0.97	0.93	0.91	0.80	0.95	0.99
	right	1.05	0.99	1.06	0.95	0.81	0.12	0.81	0.10	0.86	0.65	0.87	0.78
Rostral-middlefrontal	left	1.01	1.00	1.01	0.98	0.98	0.97	0.97	0.89	1.07	0.95	1.11	0.84
	right	0.99	1.00	0.98	0.98	0.96	0.85	0.95	0.79	0.90	0.78	0.95	0.99
Superior-frontal	left	0.92	0.82	0.92	0.90	1.02	0.97	1.02	0.97	1.03	0.95	1.06	0.96
	right	0.93	0.98	0.93	0.90	0.95	0.82	0.95	0.79	1.32	0.42	1.36	0.27
Superior-parietal	left	0.95	0.99	0.93	0.90	1.09	0.58	1.10	0.55	1.22	0.65	1.19	0.73
	right	1.00	1.00	1.00	0.98	1.15	0.34	1.15	0.31	1.21	0.65	1.19	0.73
Superior-temporal	left	1.06	0.99	1.08	0.90	1.21	0.12	1.20	0.15	1.22	0.65	1.20	0.73
	right	1.03	0.99	1.04	0.96	1.22	0.12	1.21	0.11	1.09	0.84	1.08	0.92
Supramarginal	left	0.96	0.99	0.96	0.96	1.14	0.34	1.14	0.31	1.19	0.65	1.19	0.73
	right	1.17	0.68	1.17	0.63	1.23	0.12	1.23	0.10	1.19	0.65	1.18	0.73
Temporalpole	left	1.01	1.00	1.01	0.98	1.01	0.97	1.01	0.97	1.13	0.77	1.14	0.78
	right	1.07	0.99	1.07	0.92	1.12	0.42	1.12	0.44	1.15	0.73	1.15	0.78
Transverse-temporal	left	0.88	0.69	0.89	0.64	1.16	0.28	1.16	0.28	1.04	0.95	1.03	1.00
	right	0.89	0.69	0.89	0.64	1.11	0.53	1.11	0.49	0.89	0.78	0.89	0.84

Table S5 Multivariate Results

		PNC		HCP		OASIS-3	
		F	q	F	q	F	q
Mahalanobis Distance							
Global	Sex	5.42	**0.02**	43.26	**2.3E-10**	13.83	**3.3E-04**
	Age	0.13	1.00	1.49	0.68	0.05	1.00
	Age-by-sex	1.17	0.31	0.61	0.55	0.80	0.52
Subcortical Volume	Sex	11.63	**6.7E-04**	44.40	**6.5E-11**	46.63	**6.5E-11**
	Age	0.10	0.90	0.53	0.90	0.46	0.90
	Age-by-sex	0.81	0.44	0.67	0.51	2.34	0.05
Surface Area	Sex	161.02	**1.2E-34**	229.86	**1.4E-46**	43.89	**9.4E-11**
	Age	0.39	0.67	3.28	0.06	16.23	**5.4E-12**
	Age-by-sex	2.67	0.07	1.40	0.25	7.18	**1.3E-05**
Cortical Thickness	Sex	0.85	0.36	1.41	0.35	1.77	0.35
	Age	0.01	0.99	0.05	0.99	14.88	**5.4E-11**
	Age-by-sex	0.55	0.58	0.07	0.94	0.60	0.66
Cosine Angle							
Global	Sex	6.83	**0.03**	1.25	0.26	1.40	0.26
	Age	4.84	**0.01**	6.14	**0.007**	1.13	0.34
	Age-by-sex	2.48	0.08	3.66	**0.03**	13.18	**3.4E-10**
Subcortical Volume	Sex	1.41	0.71	0.49	0.73	0.01	0.94
	Age	7.09	**0.001**	6.38	**0.002**	9.88	**3.3E-07**
	Age-by-sex	4.09	**0.02**	3.64	**0.03**	10.94	**1.7E-08**
Surface Area	Sex	0.06	0.81	0.06	0.81	1.32	0.75
	Age	6.30	**0.006**	2.97	0.08	0.98	0.42
	Age-by-sex	7.88	**4.0E-04**	0.85	0.43	7.33	**9.8E-06**
Cortical Thickness	Sex	9.16	**0.008**	6.61	**0.02**	1.63	0.20
	Age	55.92	**1.6E-23**	42.47	**2.8E-18**	21.38	**3.0E-16**
	Age-by-sex	2.66	0.07	1.18	0.31	1.55	0.19

Mahalanobis distance and cosine angle distributions for three independent datasets; Philadelphia Neurodevelopmental Cohort (PNC), Human Connectome Project (HCP) and Open Access Series of Imaging Studies (OASIS-3) were compared between males and females with a linear model followed by type 2 F-tests. *q* - False Discovery Rate (FDR) corrected *p*-value. Mahalanobis distances were calculated for each subject per age bin to their group (male or female) average per metric type. Cosine angles were calculated for each subject per age bin to their group (male or female) centroid on the n-dimensional sphere per metric type.

Additional cosine angle results discussion

The effects of age on cosine angle are notable for their developmental increase (and age-related decline). All of volume, surface area, and cortical thickness showed significant effects of age on cosine angle in the child and youth dataset. Cortical thickness notably showed the most prominent effects of age both in the developmental and late-life datasets.

We interpreted these findings as a 'biological validation' of this method, in that differentiation of regions in cortical architecture has been shown to increase during neurodevelopment, and such differentiation decreases in late life with age-related change. The novel aspect that we have demonstrated here is that across an entire group, variability across individuals in relationships among regions increases during development, and (in cortical thickness) decreases in late life. When TBV was accounted for, age effects were stronger and more widespread across datasets and metrics.

Additional results (t-tests [age regressed out] and linear models [TBV regressed out]) Mahalanobis Distance

Table S6 Mahalanobis Distance - T-tests - Age regressed out (TBV not regressed)

	PNC			HCP			OASIS-3		
	t	q	d	t	q	d	t	q	d
Global Volume	-2.53	**0.02**	-0.14	-6.39	**1.1E-09**	-0.42	-4.64	**9.0E-06**	-0.43
Subcortical Volume	-3.96	**1.1E-04**	-0.22	-6.90	**3.6E-11**	-0.44	-6.86	**4.6E-11**	-0.64
Surface Area	-12.99	**7.1E-36**	-0.75	-15.78	**1.4E-49**	-1.01	-10.30	**1.9E-22**	-0.95
Cortical Thickness	-1.29	0.26	-0.07	1.35	0.26	0.08	2.07	0.15	0.18

Table S7 Mahalanobis distance - linear model - (TBV regressed out)

		PNC		HCP		OASIS-3	
		F	q	F	q	F	q
Global	Sex	5.30	**0.03**	17.67	**8.6E-05**	1.60	0.21
	Age	0.29	0.75	1.02	0.54	4.92	**0.002**
	Age-by-sex	0.05	0.95	0.12	0.89	0.40	0.81
Subcortical Volume	Sex	16.32	**5.7E-05**	41.10	**6.6E-10**	39.86	**9.3E-10**
	Age	0.06	0.94	0.72	0.94	0.37	0.94
	Age-by-sex	0.56	0.57	0.76	0.47	2.42	**0.047**
Surface Area	Sex	159.07	**2.8E-34**	234.65	**2.0E-47**	21.75	**4.1E-06**
	Age	0.46	0.63	3.53	**0.04**	3.26	**0.04**
	Age-by-sex	2.23	0.11	1.43	0.24	3.59	**0.007**
Cortical Thickness	Sex	0.93	0.34	1.24	0.34	1.50	0.34
	Age	0.02	0.98	0.03	0.98	4.29	**0.006**
	Age-by-sex	0.57	0.57	0.09	0.92	3.21	**0.01**

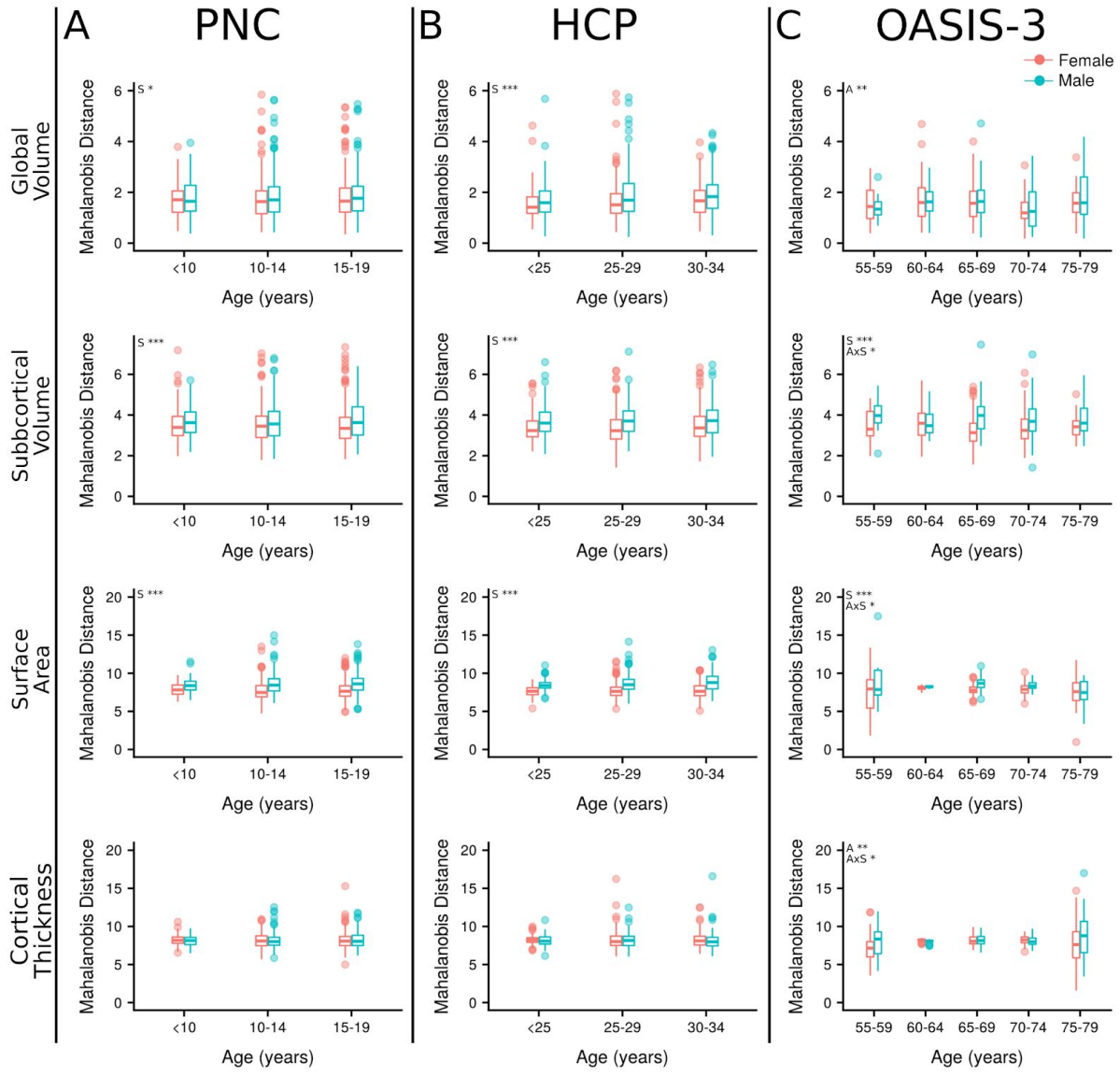

Figure S2 Mahalanobis distance (TBV regressed out)

S – sex, A – age, AxS – age-by-sex interaction, * $q < 0.05$, ** $q < 0.01$, *** $q < 0.001$.

Cosine dissimilarity

Table S8 Cosine dissimilarity - t-test - Age regressed out (TBV not regressed)

	PNC			HCP			OASIS-3		
	t	q	d	t	q	d	t	q	d
Global Volume	1.31	0.35	0.07	0.13	0.90	0.01	1.20	0.35	0.11
Subcortical Volume	0.08	0.93	0.004	-0.33	0.93	-0.02	0.59	0.93	0.05
Surface Area	-1.00	0.37	-0.05	-0.89	0.37	-0.05	1.22	0.37	0.11
Cortical Thickness	1.33	0.18	0.07	1.39	0.18	0.09	1.33	0.18	0.12

Table S9 Cosine dissimilarity - linear model - (TBV regressed out)

		PNC		HCP		OASIS-3	
		F	q	F	q	F	q
Global	Sex	0.21	0.65	4.78	**0.04**	8.92	**0.009**
	Age	54.44	**6.1E-23**	50.37	**2.0E-21**	2.45	0.05
	Age-by-sex	6.37	**0.002**	1.08	0.34	1.51	0.20
Subcortical Volume	Sex	2.50	0.26	0.13	0.72	1.88	0.26
	Age	55.37	**2.6E-23**	8.40	**2.4E-04**	9.86	**1.7E-07**
	Age-by-sex	3.74	**0.02**	0.28	0.75	3.72	**0.005**
Surface Area	Sex	0.36	0.75	0.10	0.75	6.12	**0.04**
	Age	42.51	**4.0E-18**	14.27	**7.7E-07**	10.64	**4.3E-08**
	Age-by-sex	4.77	**0.009**	7.38	**0.001**	2.91	**0.02**
Cortical Thickness	Sex	4.66	0.05	5.26	0.05	2.42	0.12
	Age	52.65	**3.2E-22**	25.75	**1.8E-11**	10.06	**7.9E-08**
	Age-by-sex	5.93	**0.003**	8.93	**1.4E-04**	5.45	**2.7E-04**

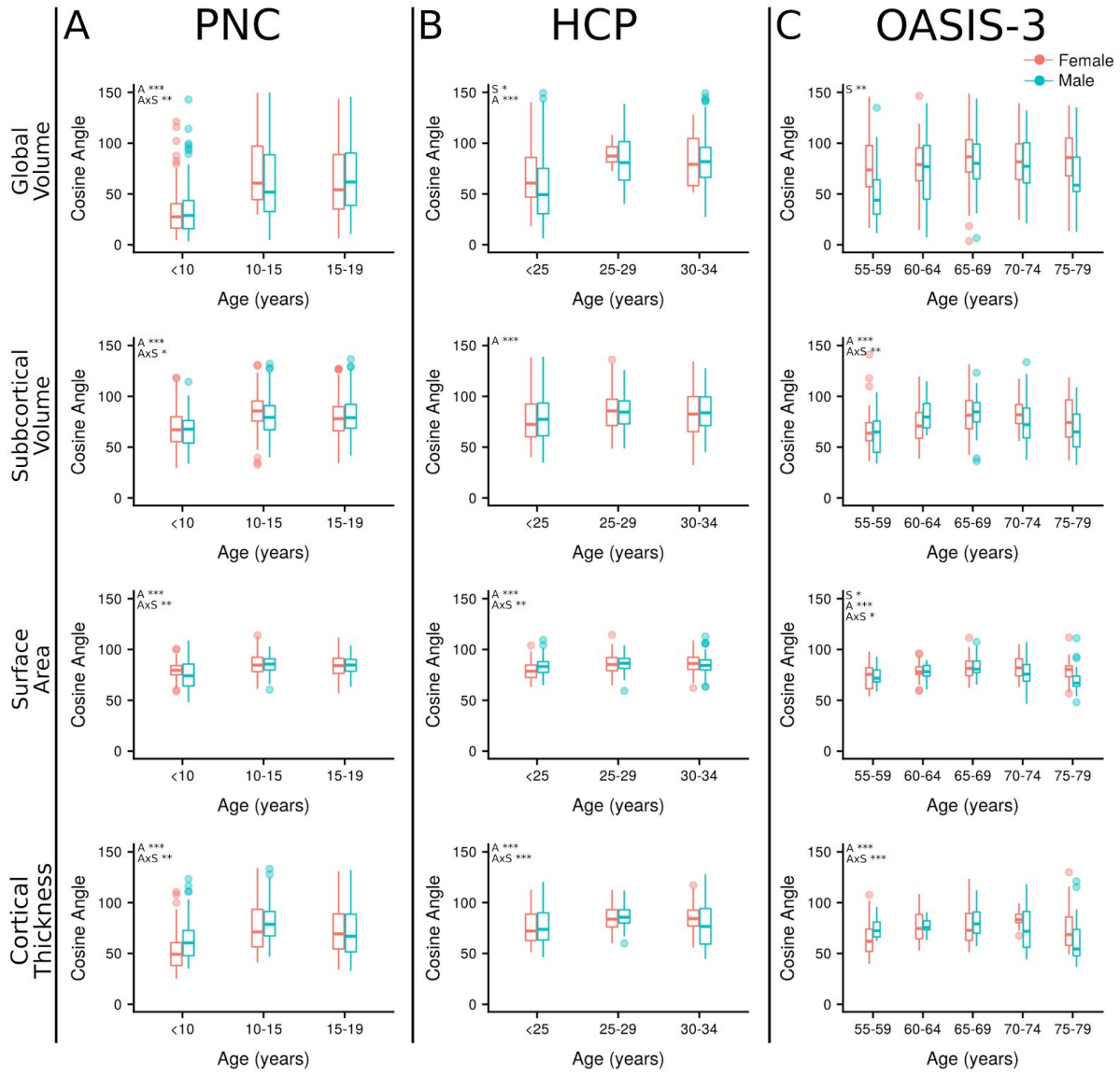

Figure S3 Cosine dissimilarity (TBV regressed out)

S – sex, A – age, AxS – age-by-sex interaction, * $q < 0.05$, ** $q < 0.01$, *** $q < 0.001$.

Matching and Verification

Matching samples based on age (MatchIt, propensity scoring) had minimal impact on VR analysis (data not shown), therefore results from the full samples are reported in the main manuscript. For both multivariate analyses age bins were used which ensures differences in the overall age distributions would not affect findings.

Mean sex effects

T-tests were conducted to examine the difference on average between males and females. To evaluate the effect size of these differences we calculated Cohen's d (T statistic * 2 / $\sqrt{}$ degrees of freedom).

Volume

Global and subcortical volumes were consistently higher in males compared to females on average, with medium to large effect sizes across all datasets (Tables S10 & S11, Figure S4). Accounting for TBV rendered the majority of these non-significant, however cerebellar grey matter (all datasets), bilateral pallidum (PNC), left amygdala (PNC and HCP) and right amygdala (HCP) volumes remaining significantly larger in males compared to females. In contrast, the right hippocampus in PNC was larger in females compared to males after TBV correction (Cohen's d = 0.15).

Table S10 Mean differences in global volumes

		PNC			HCP			OASIS-3		
		t	q	d	t	q	d	t	q	d
TBV	raw	-23.29	**2.5E-99**	-1.31	-25.59	**7.1E-111**	-1.62	-24.66	**1.1E-102**	-1.63
Cerebral GM	raw	-22.71	**2.6E-95**	-1.28	-25.23	**1.1E-108**	-1.58	-24.18	**8.4E-100**	-1.59
	corrected	-1.61	0.25	-0.09	-1.77	0.13	-0.11	-1.44	0.19	-0.10
Cerebral WM	raw	-20.74	**6.3E-82**	-1.18	-22.88	**5.7E-93**	-1.45	-22.18	**6.7E-87**	-1.48
	corrected	1.12	0.33	0.06	2.01	0.11	0.13	1.72	0.15	0.11
Cerebellar GM	raw	-14.31	**6.1E-43**	-0.80	-21.62	**9.6E-86**	-1.34	-21.07	**2.7E-81**	-1.35
	corrected	-3.24	**0.01**	-0.18	-5.53	**2.0E-07**	-0.34	-5.48	**2.8E-07**	-0.35
Cerebellar WM	raw	-4.86	**1.7E-06**	-0.27	-16.37	**2.6E-53**	-1.05	-16.22	**4.2E-52**	-1.07
	corrected	1.43	0.25	0.08	-1.42	0.20	-0.09	-1.68	0.15	-0.11

Results from analyses of sex differences in global brain volumes are presented from the Philadelphia Neurodevelopmental Cohort (PNC), Human Connectome Project (HCP) and Open Access Series of Imaging Studies (OASIS-3). Mean differences in male and female volumes were compared with age regressed out (raw) and age and total brain volume (TBV) regressed out (corrected). Mean differences were compared with a *t*-test (t). Positive Cohen's d (d) represents females > males while negative represents males > females on average.

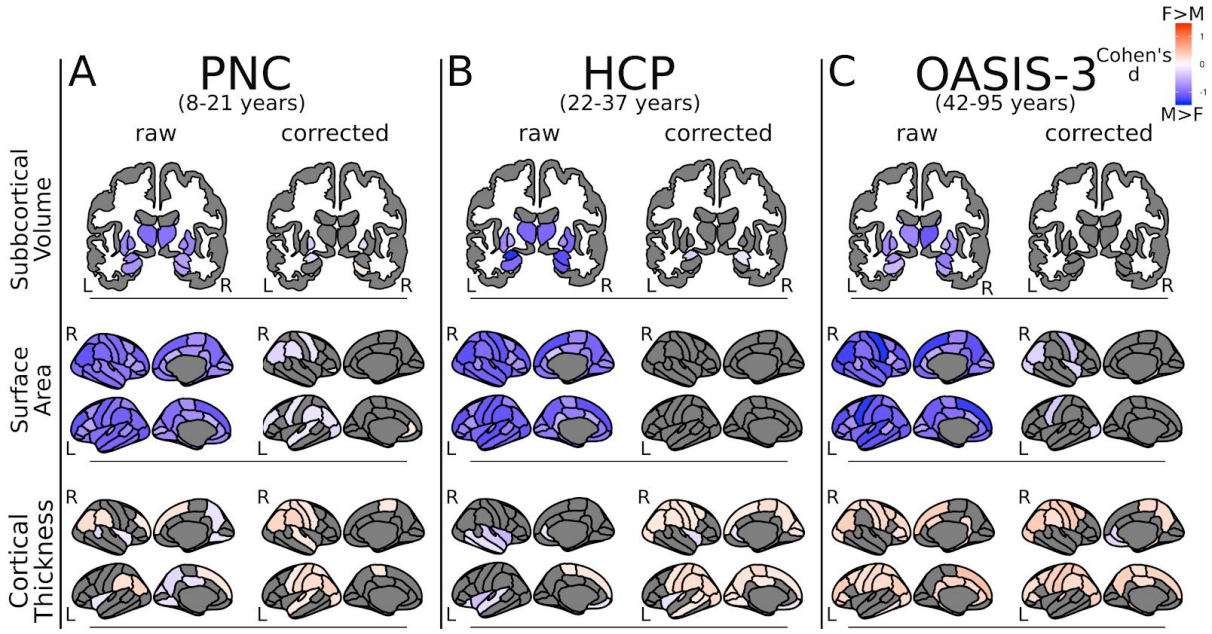

Figure S4 Average sex differences

Cohen's d effect sizes are mapped onto subcortical structures (top row) or cortical surface (middle and bottom panels) for three independent datasets; (A) The Philadelphia Neurodevelopmental Cohort (PNC), (B) The Human Connectome Project (HCP) and (C) The Open Access Series of Imaging Studies (OASIS-3). These results were generated with *t*-tests to compare average differences in subcortical volume, cortical surface area and cortical thickness between males and females. Only Cohen's d from tests that met statistical significance are plotted (q<0.05). Cohen's d > 0 (red) indicates females > males, Cohen's d < 0 (blue) indicates males (M) > females (F). 'Raw' figures show results from analyses that used metrics corrected for age (age effects regressed out). Corresponding 'corrected' figures show results from analyses that used metrics corrected for total brain volume (TBV) as well as age. Note: Nucleus Accumbens is not included in the figure but does show significant volume differences on average between males and females (males larger) across all samples in the raw analysis (see Table S11). L- left, R - right.

Table S11 Mean differences in subcortical volumes

			PNC			HCP			OASIS-3		
			t	q	d	t	q	d	t	q	d
Thalamus	left	raw	-17.67	**1.7E-61**	-0.99	-16.48	**7.5E-54**	-1.03	-8.96	**3.4E-17**	-0.82
		corrected	-1.07	0.45	-0.06	1.78	0.15	0.11	-0.09	0.93	-0.01
	right	raw	-16.87	**8.7E-57**	-0.96	-16.26	**1.4E-52**	-1.03	-11.45	**2.5E-25**	-1.14
		corrected	0.10	0.92	0.01	1.25	0.28	0.08	-0.65	0.88	-0.06
Caudate	left	raw	-11.16	**1.4E-27**	-0.63	-10.79	**9.2E-26**	-0.67	-6.18	**2.1E-09**	-0.61
		corrected	0.53	0.69	0.03	2.10	0.08	0.13	0.15	0.93	0.01
	right	raw	-11.59	**2.2E-29**	-0.65	-11.80	**3.9E-30**	-0.74	-7.31	**2.6E-12**	-0.71
		corrected	-1.22	0.39	-0.07	1.54	0.19	0.10	-0.58	0.88	-0.06
Putamen	left	raw	-14.12	**8.7E-42**	-0.80	-13.08	**3.5E-36**	-0.80	-7.88	**7.5E-14**	-0.76
		corrected	-1.66	0.23	-0.09	-1.60	0.19	-0.10	-0.85	0.79	-0.08
	right	raw	-14.95	**5.9E-46**	-0.84	-16.55	**3.0E-54**	-1.02	-7.54	**7.4E-13**	-0.75
		corrected	-1.55	0.24	-0.09	-2.21	0.08	-0.14	-0.99	0.79	-0.10
Pallidum	left	raw	-14.83	**1.8E-45**	-0.84	-9.99	**1.5E-22**	-0.61	-8.00	**3.8E-14**	-0.75
		corrected	-6.02	**3.2E-08**	-0.34	-2.15	0.08	-0.13	-2.78	0.08	-0.26
	right	raw	-13.56	**6.9E-39**	-0.77	-12.23	**3.8E-32**	-0.75	-5.95	**7.0E-09**	-0.56
		corrected	-4.16	**2.4E-04**	-0.24	-0.46	0.76	-0.03	0.14	0.93	0.01
Hippocampus	left	raw	-13.19	**3.7E-37**	-0.73	-15.66	**3.9E-49**	-1.01	-5.03	**7.6E-07**	-0.47
		corrected	0.71	0.61	0.04	-1.22	0.28	-0.08	1.86	0.30	0.17
	right	raw	-11.54	**2.7E-29**	-0.64	-17.88	**6.9E-62**	-1.11	-6.71	**9.2E-11**	-0.64
		corrected	2.77	**0.02**	0.15	-2.16	0.08	-0.13	1.35	0.62	0.13
Amygdala	left	raw	-14.60	**2.5E-44**	-0.82	-21.62	**3.7E-84**	-1.37	-7.29	**2.6E-12**	-0.70
		corrected	-3.90	**4.7E-04**	-0.22	-5.05	**7.2E-06**	-0.32	-0.15	0.93	-0.01
	right	raw	-11.55	**2.7E-29**	-0.65	-19.20	**1.3E-69**	-1.20	-9.40	**2.1E-18**	-0.89
		corrected	-1.65	0.23	-0.09	-2.85	**0.03**	-0.18	-2.06	0.28	-0.19
Nucleus Accumbens	left	raw	-4.35	**1.5E-05**	-0.24	-13.11	**3.1E-36**	-0.82	-3.77	**1.8E-04**	-0.35
		corrected	-0.99	0.45	-0.06	-0.33	0.77	-0.02	-0.92	0.79	-0.09
	right	raw	-8.54	**4.0E-17**	-0.48	-13.40	**1.2E-37**	-0.84	-5.48	**8.4E-08**	-0.52
		corrected	-0.29	0.83	-0.02	-0.29	0.77	-0.02	-0.46	0.91	-0.04

Results from analyses of sex differences in subcortical brain volumes are presented from the Philadelphia Neurodevelopmental Cohort (PNC), Human Connectome Project (HCP) and Open Access Series of Imaging Studies (OASIS-3). Mean differences in male and female volumes were compared with age regressed out (raw) and age and total brain volume (TBV) regressed out (corrected). Mean differences were compared with a *t*-test (t). Positive Cohen's d (d) represents females > males while negative represents males > females on average.

Surface area

Similarly, SA was significantly higher in males compared to females across the cortex in all datasets, accounting for TBV again reduced these effects. However, some regions did remain significantly larger in males compared to females in the PNC (12 regions) and OASIS-3 samples (10 regions) datasets (Figure S4). Following TBV correction there was also one region in the development sample (PNC) where SA was significantly greater in females; left rostral anterior cingulate (Cohen's d 0.16, q<0.05, Figure S4).

Cortical Thickness

Results from the analysis of CT was more variable across datasets. Females had greater CT than males in various regions across all datasets with small to medium effect sizes. While males also displayed greater CT than females in certain regions (Figure S4). Accounting for TBV reduced the extent of differences where males were greater than females and increased the number of regions where females had significantly larger CT than males.

Supplementary Discussion

Genetics

We speculate that mechanisms involved in the early propagation of intermediate radial glia cells, which are involved in the tangential expansion of the cortex [7], may be related to the variability differences seen in surface area between the sexes. The animal literature provides hints as to how these sex differences may arise as it has been shown that the estrogen steroid hormone estradiol, which is the major female sex hormone, promotes the proliferation of progenitor cells during development [8]. Additionally, there is evidence that hormones modulate epigenetic regulation during development [9]. Recent work on sex-chromosome aneuploidy has indicated a dose effect of sex-chromosomes on gene expression [12]. Additional work from the same group has found effects of sex-chromosome dosage on brain structures [13, 14]. These studies show sex-chromosomes influence both brain structure and gene-expression, however, further work is required to identify the underlying causes of the discrepancy in variability between males and females seen here and determine the relationship to genetic variability or gene expression.

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