

Supplementary Materials for

An uncertainty-aware, shareable, and transparent neural network architecture for brain-age modeling

Tim Hahn*, Jan Ernsting, Nils R. Winter, Vincent Holstein, Ramona Leenings, Marie Beisemann, Lukas Fisch, Kelvin Sarink, Daniel Emden, Nils Opel, Ronny Redlich, Jonathan Repple, Dominik Grotegerd, Susanne Meinert, Jochen G. Hirsch, Thoralf Niendorf, Beate Endemann, Fabian Bamberg, Thomas Kröncke, Robin Bülow, Henry Völzke, Oyunbileg von Stackelberg, Ramona Felizitas Sowade, Lale Umutlu, Børge Schmidt, Svenja Caspers, Harald Kugel, Tilo Kircher, Benjamin Risse, Christian Gaser, James H. Cole, Udo Dannlowski, Klaus Berger

*Corresponding author. Email: hahnt@wwu.de

Published 5 January 2022, *Sci. Adv.* **8**, eabg9471 (2022)
DOI: 10.1126/sciadv.abg9471

This PDF file includes:

Supplementary Text
Figs. S1 to S3
Tables S1 and S2

Supplementary Text

To assess the effects of modeling aleatory and epistemic uncertainty, we investigated PICPs for 1) the MCCQR approach modeling both aleatory and epistemic uncertainty, 2) a version of our model accounting for aleatory uncertainty only, and 3) a version of our model modeling epistemic uncertainty only.

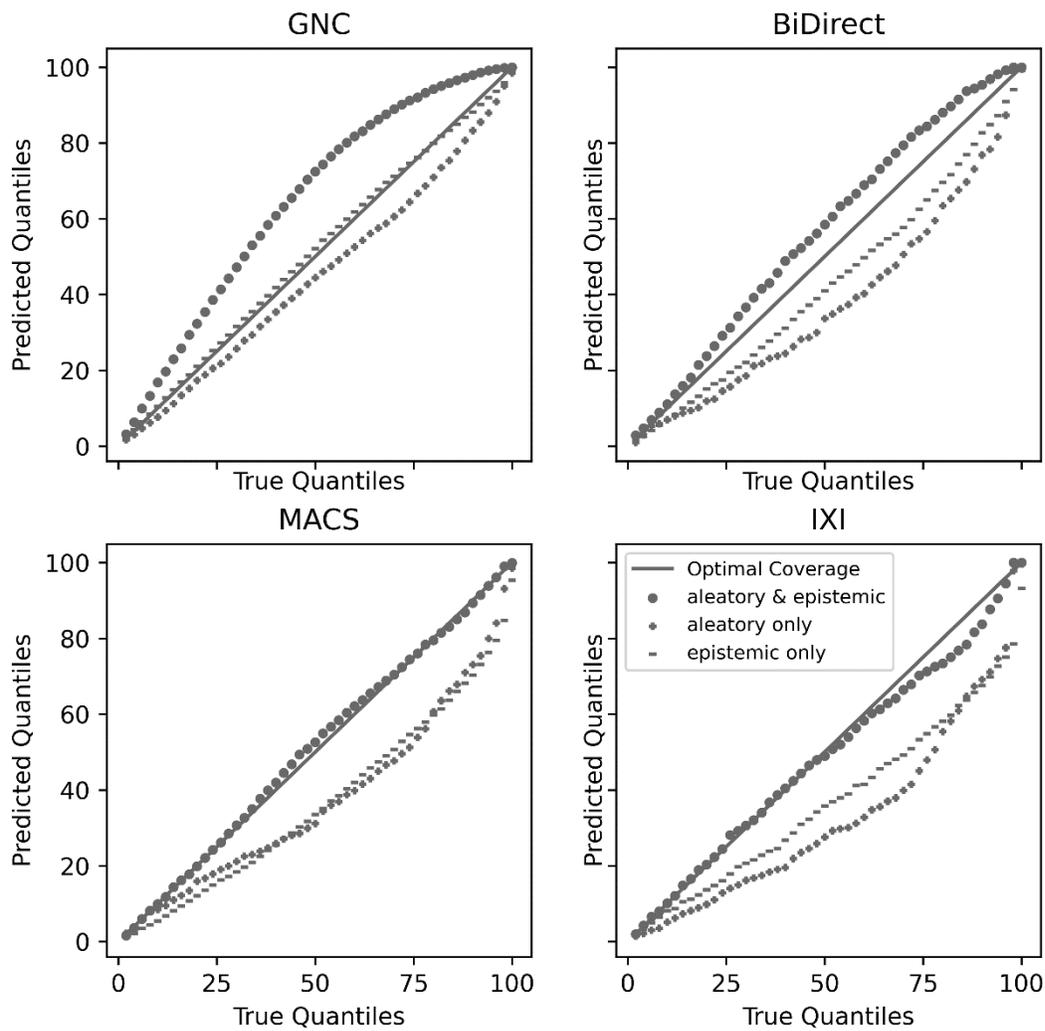
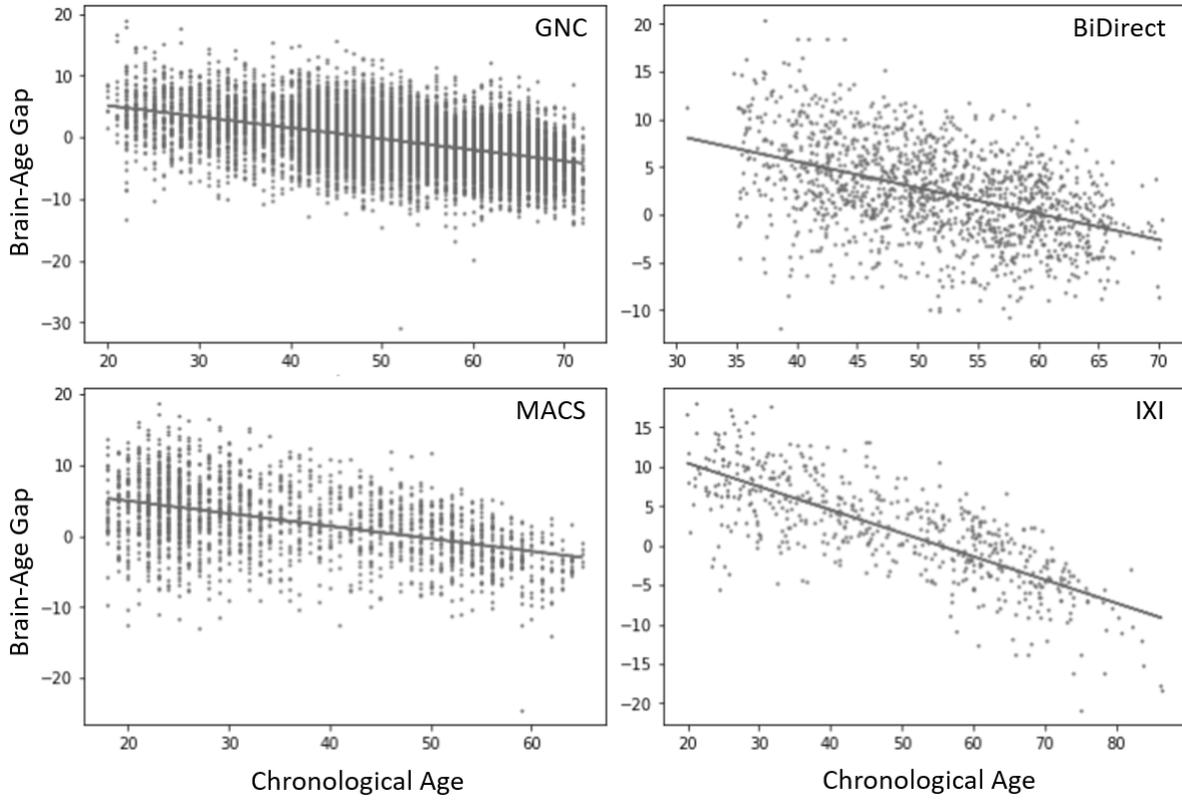


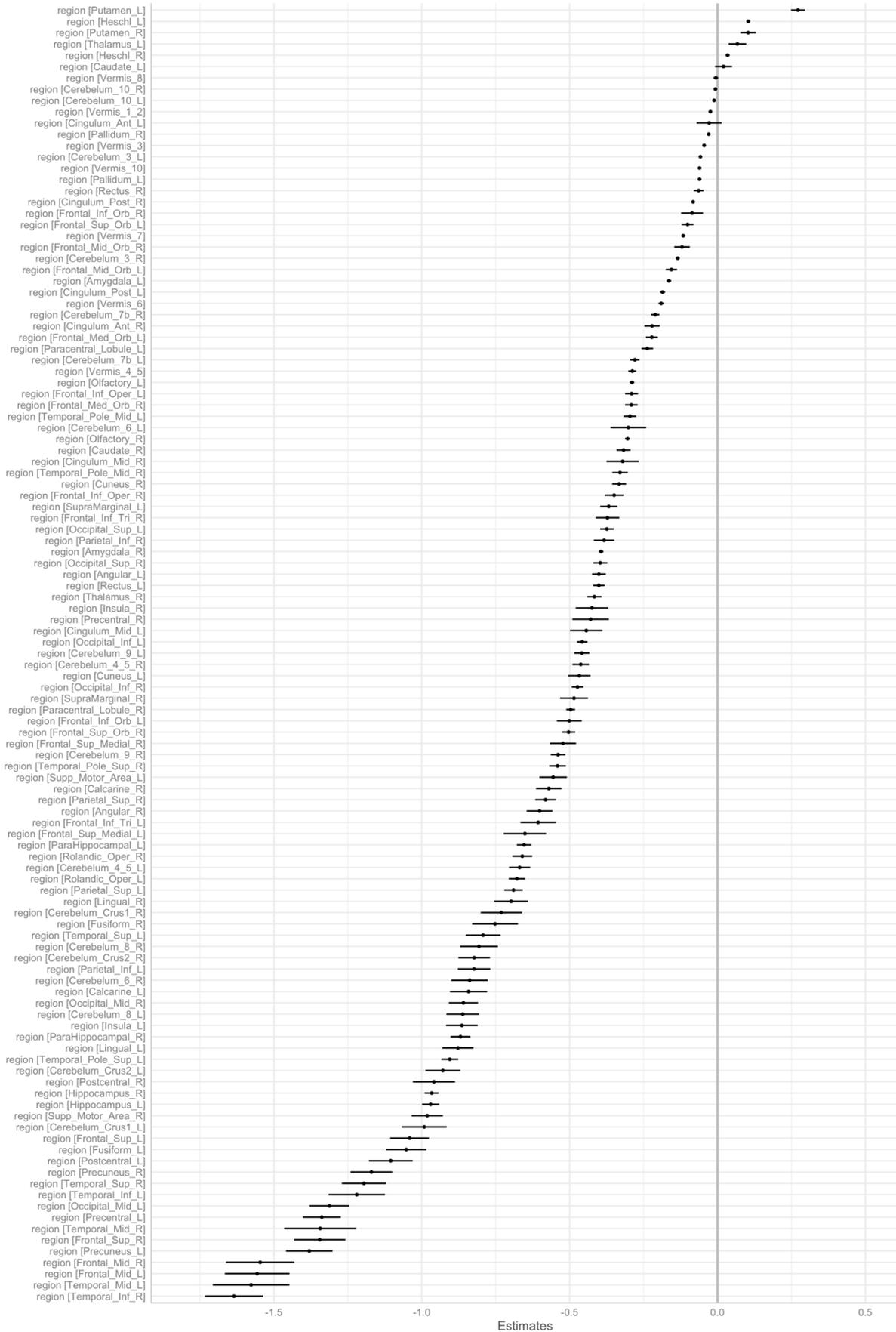
Fig. S1.

Supplementary Figure S1. Prediction Interval Coverage Probabilities (PICP) for leave-site-out GNC and independent validation samples (BiDirect, MACS, and IXI) for modeling 1) aleatory uncertainty only, 2) epistemic uncertainty only, and 3) both aleatory and epistemic uncertainty. Underestimation (overestimation) of uncertainty occurs, if empirical PICPs are below (above) optimal PICP as indicated by the solid line.



Supplementary Figure S2. Scatter plot showing the association between brain-age gap and chronological age for GNC, BiDirect, MACS, and IXI.

BAGz



Supplementary Figure S3. Fixed effect estimates for AAL region of interests of the Occlusion-Sensitivity Mapping analysis. Estimates can be interpreted as difference from the whole brain, not occluded model. Error bars indicate +/- 1 standard deviation.

<i>Predictors</i>	<i>Estimates</i>	BAGz	
		<i>CI</i>	<i>p</i>
(Intercept)	0.97	0.92, 1.02	<0.001
age	-0.37	-0.40, -0.34	<0.001
gender	0.08	0.05, 0.11	<0.001
site	0.22	0.18, 0.25	<0.001
ROI size	0.41	0.38, 0.44	<0.001
region Amygdala_L	-0.16	-0.17, -0.16	<0.001
region Amygdala_R	-0.39	-0.40, -0.39	<0.001
region Angular_L	-0.40	-0.42, -0.38	<0.001
region Angular_R	-0.60	-0.65, -0.56	<0.001
region Calcarine_L	-0.84	-0.90, -0.78	<0.001
region Calcarine_R	-0.57	-0.61, -0.53	<0.001
region Caudate_L	0.02	-0.01, 0.05	0.167
region Caudate_R	-0.32	-0.34, -0.29	<0.001
region Cerebellum_10_L	-0.01	-0.02, -0.01	<0.001
region Cerebellum_10_R	-0.01	-0.01, -0.00	0.022
region Cerebellum_3_L	-0.06	-0.06, -0.05	<0.001
region Cerebellum_3_R	-0.13	-0.14, -0.13	<0.001
region Cerebellum_4_5_L	-0.67	-0.71, -0.63	<0.001
region Cerebellum_4_5_R	-0.46	-0.49, -0.43	<0.001
region Cerebellum_6_L	-0.30	-0.36, -0.24	<0.001
region Cerebellum_6_R	-0.84	-0.90, -0.78	<0.001
region Cerebellum_7b_L	-0.28	-0.30, -0.26	<0.001
region Cerebellum_7b_R	-0.21	-0.22, -0.20	<0.001
region Cerebellum_8_L	-0.86	-0.92, -0.81	<0.001
region Cerebellum_8_R	-0.81	-0.87, -0.74	<0.001
region Cerebellum_9_L	-0.46	-0.48, -0.43	<0.001
region Cerebellum_9_R	-0.54	-0.56, -0.51	<0.001
region Cerebellum_Crus1_L	-0.99	-1.07, -0.92	<0.001
region Cerebellum_Crus1_R	-0.73	-0.80, -0.66	<0.001
region Cerebellum_Crus2_L	-0.93	-0.99, -0.87	<0.001
region Cerebellum_Crus2_R	-0.82	-0.88, -0.77	<0.001
region Cingulum_Ant_L	-0.03	-0.07, 0.01	0.186
region Cingulum_Ant_R	-0.22	-0.25, -0.20	<0.001
region Cingulum_Mid_L	-0.44	-0.50, -0.39	<0.001
region Cingulum_Mid_R	-0.32	-0.38, -0.27	<0.001
region Cingulum_Post_L	-0.19	-0.19, -0.18	<0.001
region Cingulum_Post_R	-0.08	-0.09, -0.08	<0.001
region Cuneus_L	-0.47	-0.51, -0.43	<0.001
region Cuneus_R	-0.33	-0.36, -0.31	<0.001
region Frontal_Inf_Oper_L	-0.29	-0.31, -0.27	<0.001
region Frontal_Inf_Oper_R	-0.35	-0.38, -0.32	<0.001
region Frontal_Inf_Orb_L	-0.50	-0.54, -0.46	<0.001
region Frontal_Inf_Orb_R	-0.09	-0.12, -0.05	<0.001
region Frontal_Inf_Tri_L	-0.61	-0.67, -0.55	<0.001
region Frontal_Inf_Tri_R	-0.37	-0.41, -0.33	<0.001
region Frontal_Med_Orb_L	-0.22	-0.24, -0.20	<0.001
region Frontal_Med_Orb_R	-0.29	-0.31, -0.27	<0.001
region Frontal_Mid_L	-1.56	-1.67, -1.45	<0.001
region Frontal_Mid_Orb_L	-0.16	-0.17, -0.14	<0.001
region Frontal_Mid_Orb_R	-0.12	-0.15, -0.09	<0.001
region Frontal_Mid_R	-1.55	-1.66, -1.43	<0.001
region Frontal_Sup_L	-1.04	-1.11, -0.98	<0.001
region Frontal_Sup_Medial_L	-0.65	-0.72, -0.58	<0.001
region Frontal_Sup_Medial_R	-0.52	-0.57, -0.48	<0.001
region Frontal_Sup_Orb_L	-0.10	-0.12, -0.08	<0.001
region Frontal_Sup_Orb_R	-0.50	-0.53, -0.48	<0.001

region Frontal_Sup_R	-1.35	-1.43, -1.26	<0.001
region Fusiform_L	-1.05	-1.12, -0.98	<0.001
region Fusiform_R	-0.75	-0.83, -0.67	<0.001
region Heschl_L	0.10	0.10, 0.11	<0.001
region Heschl_R	0.03	0.03, 0.04	<0.001
region Hippocampus_L	-0.97	-1.00, -0.94	<0.001
region Hippocampus_R	-0.97	-0.99, -0.94	<0.001
region Insula_L	-0.86	-0.92, -0.81	<0.001
region Insula_R	-0.42	-0.48, -0.37	<0.001
region Lingual_L	-0.88	-0.93, -0.83	<0.001
region Lingual_R	-0.70	-0.76, -0.64	<0.001
region Occipital_Inf_L	-0.46	-0.48, -0.44	<0.001
region Occipital_Inf_R	-0.47	-0.49, -0.45	<0.001
region Occipital_Mid_L	-1.31	-1.38, -1.25	<0.001
region Occipital_Mid_R	-0.86	-0.91, -0.81	<0.001
region Occipital_Sup_L	-0.37	-0.40, -0.35	<0.001
region Occipital_Sup_R	-0.40	-0.42, -0.37	<0.001
region Olfactory_L	-0.29	-0.30, -0.28	<0.001
region Olfactory_R	-0.30	-0.31, -0.30	<0.001
region Pallidum_L	-0.06	-0.07, -0.05	<0.001
region Pallidum_R	-0.03	-0.04, -0.02	<0.001
region Paracentral_Lobule_L	-0.24	-0.26, -0.22	<0.001
region Paracentral_Lobule_R	-0.50	-0.51, -0.48	<0.001
region ParaHippocampal_L	-0.65	-0.68, -0.63	<0.001
region ParaHippocampal_R	-0.87	-0.90, -0.84	<0.001
region Parietal_Inf_L	-0.82	-0.88, -0.77	<0.001
region Parietal_Inf_R	-0.38	-0.42, -0.35	<0.001
region Parietal_Sup_L	-0.69	-0.72, -0.66	<0.001
region Parietal_Sup_R	-0.58	-0.62, -0.55	<0.001
region Postcentral_L	-1.10	-1.18, -1.03	<0.001
region Postcentral_R	-0.96	-1.03, -0.89	<0.001
region Precentral_L	-1.34	-1.40, -1.27	<0.001
region Precentral_R	-0.43	-0.49, -0.37	<0.001
region Precuneus_L	-1.38	-1.46, -1.30	<0.001
region Precuneus_R	-1.17	-1.24, -1.10	<0.001
region Putamen_L	0.27	0.25, 0.30	<0.001
region Putamen_R	0.10	0.08, 0.13	<0.001
region Rectus_L	-0.40	-0.42, -0.38	<0.001
region Rectus_R	-0.06	-0.08, -0.05	<0.001
region Rolandic_Oper_L	-0.68	-0.71, -0.65	<0.001
region Rolandic_Oper_R	-0.66	-0.69, -0.63	<0.001
region Supp_Motor_Area_L	-0.56	-0.60, -0.51	<0.001
region Supp_Motor_Area_R	-0.98	-1.03, -0.93	<0.001
region SupraMarginal_L	-0.37	-0.40, -0.34	<0.001
region SupraMarginal_R	-0.49	-0.53, -0.44	<0.001
region Temporal_Inf_L	-1.22	-1.32, -1.12	<0.001
region Temporal_Inf_R	-1.63	-1.73, -1.54	<0.001
region Temporal_Mid_L	-1.58	-1.71, -1.45	<0.001
region Temporal_Mid_R	-1.34	-1.47, -1.22	<0.001
region Temporal_Pole_Mid_L	-0.30	-0.32, -0.27	<0.001
region Temporal_Pole_Mid_R	-0.33	-0.36, -0.30	<0.001
region Temporal_Pole_Sup_L	-0.91	-0.93, -0.88	<0.001
region Temporal_Pole_Sup_R	-0.54	-0.57, -0.51	<0.001
region Temporal_Sup_L	-0.79	-0.85, -0.73	<0.001
region Temporal_Sup_R	-1.20	-1.27, -1.12	<0.001
region Thalamus_L	0.07	0.04, 0.10	<0.001
region Thalamus_R	-0.42	-0.44, -0.39	<0.001
region Vermis_1_2	-0.02	-0.03, -0.02	<0.001
region Vermis_10	-0.06	-0.07, -0.05	<0.001
region Vermis_3	-0.05	-0.05, -0.04	<0.001

region Vermis_4_5	-0.29	-0.30, -0.27	<0.001
region Vermis_6	-0.19	-0.20, -0.18	<0.001
region Vermis_7	-0.12	-0.12, -0.11	<0.001
region Vermis_8	-0.01	-0.01, 0.00	0.154
Random Effects			
σ^2	0.01		
τ_{00} Subject_ID	0.52		
ICC	0.98		
N _{Subject_ID}	1986		
Observations	232362		
Marginal R ² / Conditional R ²	0.291 / 0.984		

Supplementary Table S1. Results of the General Multi-Level Model for Occlusion-Sensitivity Mapping. CI = confidence intervals, σ^2 = variance of random effect, ICC = intra class correlation coefficient, N = number of samples, R² = explained variance.

Sample	Group	N	N Males	Age Mean	Age Std.	Age Min.	Age Max.
GNC	Full Sample	10,691	5,485	51.79	11.37	20.00	72.00
BiDirect	Full Sample	1,460	811	51.37	8.15	30.91	70.25
	MDD	719	438	49.39	7.40	30.91	67.09
	Cardiac Event	53	41	56.96	5.97	43.18	66.54
	Population Sample	688	361	53.01	8.48	35.19	70.25
MACS	Full Sample	1,986	1,259	35.87	13.03	18.00	65.00
	HC	924	595	34.16	12.88	18.00	65.00
	MDD	822	537	36.51	13.18	18.00	65.00
	BD	131	71	41.76	11.73	20.00	64.00
	SZ	66	35	38.03	11.08	18.00	57.00
	SA	43	25	38.91	13.15	18.00	63.00
IXI	HC	561	311	48.62	16.49	19.98	86.32
Beijing Normal University	HC	179	107	21.25	1.92	18.00	28.00

Supplementary Table S2. Overview of sample and subsample distributions. Std.: Standard Deviation, Min.: Minimum, Max.: Maximum, HC: Healthy Controls, MDD: Major Depressive Disorder, BD: Bipolar Disorder, SZ: Schizophrenia, SA: Schizoaffective Disorder)