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Regional adiposity shapes brain and cognition in adults

In the format provided by the authors and unedited

Supplementary Materials

Supplementary Methods

Exclusion Criteria of Participant Selection

The major physical illnesses, neurological or psychiatric diseases included cancer, dementia or Alzheimer's disease, Parkinson's disease, chronic degenerative neurological diseases, Guillain-Barré syndrome, multiple sclerosis, other demyelinating diseases, stroke or ischemic stroke, brain haemorrhage, brain or intracranial abscess, cerebral aneurysm, cerebral palsy, encephalitis, epilepsy, head injury, infections of the nervous system, meningioma, meningitis, motor neuron disease, neurological injury or trauma, spina bifida, subdural hematoma, subarachnoid haemorrhage, transient ischemic attack, angina pectoris, acute myocardial infarction, certain current complications following acute myocardial infarction, other acute ischemic heart diseases, chronic ischaemic heart disease, occlusion and stenosis of precerebral arteries, cerebrovascular disorders, sequelae of cerebrovascular disease, schizophrenia, bipolar disorder, depression, and stress-related disorders.

MRI Quality Control

MRI quality control (QC) procedures were conducted after excluding participants with major physical, neurological, or psychiatric diseases, and were applied to participants with available structural, functional, or diffusion MRI data. Each imaging modality underwent a dedicated QC process tailored to its specific artifacts and acquisition characteristics.

1. For T1-weighted MRI, scans with severe motion, severe bias-field, incomplete brain coverage and other acquisition artefact were discarded [1]. The remaining scans were processed with FreeSurfer v6.0 (longitudinal recon-all), and each segmentation was visually inspected for skull-strip errors, pervasive sulcal over- or under-segmentation, and large-scale cortical misclassification.
2. For resting-state functional MRI (rsfMRI) after preprocessing with the FSL (version 5.0.10) pipeline, scans with a mean framewise displacement (FD) greater than 0.5 mm or more than 20 volumes exceeding a head motion threshold of 0.1 mm were excluded to minimize motion artifacts [2,3]; additional exclusions were made for failed fMRI to residual ghosting or spikes and failed fMRI to T1 co-registration on visual inspection.

3. Diffusion MRI data were first screened for severe artefacts, including gradient dropout and failures in top-up algorithm, eddy correction, or model fitting [4]. Scans exhibiting these issues were excluded. For the remaining datasets, preprocessing was performed using FSL's eddy with outlier replacement enabled. Additional exclusion criteria included: (1) more than 5% of slices replaced due to outliers [5], (2) mean residual error exceeding 0.5, and (3) more than 10% of white matter voxels exhibiting unphysical NDI or ODI values [6]. Following automated QC, all retained scans underwent visual inspection to identify residual artefacts such as striping or tract-level distortions.

Detailed reasons and counts for MRI quality control exclusions are summarized in **Supplementary Table 7**, while the overall participant selection process is illustrated in the flowchart (**Supplementary Fig. 1**)

Brain Morphological Analysis

Raw T1-weighted MRI data obtained from UK Biobank underwent minimal preprocessing to ensure spatial alignment and brain tissue extraction. The initial steps included defacing for subject anonymity, reducing the field-of-view to exclude non-brain tissue, and applying gradient distortion correction. Skull stripping was carried out using the watershed algorithm included in FreeSurfer's recon-all pipeline, followed by linear registration to the MNI152 standard space using FLIRT. Nonlinear registration to the MNI152 space was performed using FNIRT to refine alignment. The resulting transformation matrix was used to invert the standard-space brain mask into the individual's native space, allowing generation of brain-extracted T1 images in native space.

Subsequent processing of T1-weighted MRI data utilized the FreeSurfer longitudinal analysis pipeline (version 6.0), which improves the reliability and consistency of morphometric estimates, even when applied to single-time-point data [7,8]. Brain morphology was quantified across cortical thickness, cortical volume, surface area, and subcortical volumes. For subcortical analysis, 14 regions of interest (ROIs) were defined based on the 'aseg' parcellation scheme, including bilateral nucleus accumbens, caudate, putamen, globus pallidus, thalamus, hippocampus, and amygdala. For cortical metrics, voxel-wise registration to the FreeSurfer template was performed, and data were smoothed with a Gaussian kernel (10 mm FWHM) to improve signal-to-noise ratios and minimize misregistration artifacts.

Functional Network Analysis

The preprocessing of resting-state fMRI (rsfMRI) data followed standard protocols to ensure robust signal extraction and alignment. Initial steps included slice timing correction, zero padding, motion correction, and intensity normalization using FSL tools. The fMRI images were then aligned to the corresponding T1-weighted structural images via boundary-based registration (BBR). Skull stripping was applied to remove non-brain tissues, followed by regression of confounding signals such as head motion (six motion parameters), whole-brain signals, cerebrospinal fluid (CSF), and white matter. To isolate low-frequency BOLD fluctuations, a temporal band-pass filter (0.01–0.08 Hz) was applied. The processed fMRI data were then nonlinearly registered to atlas space using Large Deformation Diffeomorphic Metric Mapping (LDDMM).

For functional connectivity (FC) analysis, a Pearson's correlation matrix was generated for each participant by calculating correlations between all pairs of regions defined in Shen's atlas. Correlation coefficients were Fisher z-transformed, and to enforce sparsity, connections were thresholded at the 90th percentile. The 268 regions of interest (ROIs) defined by Shen's atlas were further grouped into 10 functional networks for higher-level analyses: the Visual (VIS), Somatomotor (SMN), Dorsal Attention (DAN), Ventral Attention (VAN), Limbic (LIM), Frontoparietal (FPN), and Default Mode networks (DMN), along with additional networks such as the Cerebellar (CER), Subcortical (SUB), and Brainstem (BST) networks.

Neurite Orientation Dispersion and Density Imaging Analysis

Diffusion-weighted imaging (DWI) data were processed to extract advanced NODDI-based microstructural parameters. Initial preprocessing included correction for eddy currents, head motion, gradient distortion, and outlier slice removal. The Neurite Orientation Dispersion and Density Imaging (NODDI) model was applied to the diffusion-weighted imaging (DWI) data using the Accelerated Microstructure Imaging via Convex Optimization (AMICO) pipeline, deriving voxel-wise microstructural parameters. These included the neurite density index (NDI) as a measure of neurite density, the isotropic volume fraction (ISOVF) as a measure of free water content, and the orientation dispersion index (ODI) as a measure of variability in fiber orientation.

The resulting NODDI metrics (NDI, ISOVF, OD) were registered to the JHU template space using the ANTs framework. The registration pipeline involved a rigid body transformation for motion correction, an affine transformation for global scaling and shearing, and a nonlinear transformation via the Symmetric Normalization (SyN) algorithm for localized deformations. Mutual Information (MI) was used as the similarity metric throughout the registration process. To enhance the signal-to-noise ratio and minimize partial volume effects, all maps were spatially smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel.

Detailed Region Assignments for Each Brian System

The brain systems—default mode network (DMN), somatomotor network (SMN), limbic network (LIM), and subcortical, cerebellar, and brainstem circuits (SUB-CER-BST)—were defined based on cortical, functional and white matter regions, which were grouped by the following strategy.

1. Cortical and Subcortical Morphometry

For DMN, SMN, and LIM, cortical metrics such as cortical thickness, cortical volume, surface area and subcortical volume were extracted based on the Yeo's 7 networks parcellation. The respective network assignments define the boundaries for each system. For the SUB-CER-BST system, only subcortical, cerebellar, and brainstem volumes will be included.

2. Functional Connectivity

Based on Yeo's 7 networks parcellation, functional connectivity (FC) within the DMN, SMN, and LIM networks was assigned to their corresponding systems. For the SUB-CER-BST system, FC within the subcortical, cerebellar, and brainstem regions was collectively assigned to the SUB-CER-BST system.

3. White Matter

White matter metrics were derived based on specific tracts mapped to each system, with the tract assignments consistent with the JHU ICBM DTI Atlas. For the DMN system-related white matter regions, the primary structures included the cingulum and corpus callosum. The SMN system-related white matter regions predominantly involved the internal capsule, corticospinal tract, and external capsule. The LIM system-related white matter regions were primarily associated with the hippocampus. Lastly, the SUB-CER-BST system-related tracts mainly comprised the cerebellar peduncle.

System-specific Brain-Age prediction model

Using the regions defined above, we next derived a brain-age prediction model independently for each system (DMN, SMN, LIM, SUB-CER-BST). For each system s, we constructed a multimodal predictor matrix $\boldsymbol{X}^{(s)}$, comprising neuroimaging features identified as significantly associated with regional adiposity measures in preceding analyses. These included vertex-level cortical morphometric indices (thickness, surface area, and volume), region-level subcortical volumes, region-to-region functional connectivity values, and voxel-wise NODDI parameters (neurite density index [NDI], orientation dispersion index [ODI], and isotropic volume fraction [ISOVF]) extracted from white matter regions. All system-specific features were concatenated into a single matrix per brain system to serve as inputs for subsequent brain-age modeling. Within every training fold the columns of $\boldsymbol{X}^{(s)}$ were *z*-standardised. Chronological age A was then modelled with a partial least-squares (PLS) regression:

$$\hat{A}^{(s)} = f_{\mathrm{PLS}}(X^{(s)}; n),$$

where n is the number of latent components. To determine n we carried out a stratified 10-fold cross-validation (i.e. nine folds for training, one for testing; each participant predicted once from unseen data): inside each outer fold we refit the model for every n =1,…,20, computed the mean absolute error (MAE) on the held-out data, and retained the n with the lowest MAE. Across folds the optimal dimensionality converged on **13 – 18 components** (median n values: SMN 15, LIM 14, DMN 16, SUB-CER-BST 18). Out-of-fold predictions yielded MAE = 2.24 – 4.53 years and R^2=0.66-0.93 (**Supplementary Fig. 5.**).

For each participant, the raw Brain-Age Gap (BAG) for system s is

$$\mathrm{BAG}_i^{(s)} = \hat{A}_i^{(s)} - A_i,$$

with $\hat{A}_i^{(s)}$ taken from each outer test fold. Because BAG usually shows a residual dependence on age, we regressed BAG on chronological age after the calculation from the model,

$$\mathrm{BAG}^{(s)} = \beta_0^{(s)} + \beta_1^{(s)} A + \varepsilon,$$

and subtracted the fitted values to obtain an age-independent gap

$$\mathrm{BAG}_i^{(s,\mathrm{adj})} = \mathrm{BAG}_i^{(s)} - \left(\beta_0^{(s)} + \beta_1^{(s)} A_i\right).$$

After correction, these system-specific, bias-free BAGs (SMN-BAG, LIM-BAG, DMN-BAG, SUB-CER-BST-BAG) were the brain-age measures carried forward to the mediation analyses reported in the main text.

Covariates

Age was constructed from Field [21003-2.0] for all participants at first imaging visit.

Sex was coded as a binary variable based on Field [31-0.0], with 0 indicating females and 1 indicating males.

Ethnicity was categorized based on Field [21000-0.0], which records participants' self-reported ethnic background. The original dataset included multiple ethnic categories; however, for this study, participants were classified into two groups: White (0) and Non-White (1). The White group encompassed codes for British (1001), Irish (1002), and any other White background (1003), while all other ethnic categories were grouped as Non-White.

Handedness was assessed using Field [1707-0.0], where participants self-reported their dominant hand as right-handed (1), left-handed (2), or ambidextrous (3). For the current study, handedness was recoded into two categories: right-handed (1) and left-handed (0).

Educational years, a marker of socioeconomic status, was inferred from Field [845-0(2).0], which records participants' highest qualification. Years of education were assigned based on the criteria defined in [9], : College or University Degree (16 years), A Levels or AS Levels (13 years), O Levels or GCSEs (11 years), National Vocational Qualification (NVQ) or professional certifications (10 years), and no formal education (0 years).

Employment status was derived from Field [6142-0(2).0] and dichotomized into employed (1) and unemployed (0). This binary classification can reflect workforce participation as a socioeconomic factor relevant to health and cognitive outcomes.

Smoking frequency was categorized using Field [1239-0(2).0], originally coded as 1 (Yes, on most or all days), 2 (Only occasionally), 0 (No), and -3 (Prefer not to answer). For this study, -

3 responses were recorded as 0, resulting in three final categories: non-smokers (0), occasional smokers (1), and daily smokers (2).

Alcohol consumption frequency was assessed via Field [1558-0(2).0], which originally included seven categories: 1 (Daily or almost daily), 2 (Three or four times a week), 3 (Once or twice a week), 4 (One to three times a month), 5 (Special occasions only), 6 (Never), and -3 (Prefer not to answer). For this study, -3 responses were recoded as 0, and the categories were reverse-coded such that higher values corresponded to higher frequency of alcohol consumption. The final categorization included six levels (0–5), with 0 representing "Never" and 5 representing "Daily or almost daily."

Physical activity levels were assessed using MET (Metabolic Equivalent Task) scores Field [22032-0(2).0], calculated according to the guidelines outlined by the International Physical Activity Questionnaire (IPAQ). The derivation of these scores is detailed in former publication [10], which aligns with the IPAQ's standardized framework for categorizing activity levels. Participants' physical activity was grouped into three categories: low (0), moderate (1), and high (2), based on the frequency and intensity of reported activity.

In June 2023, the UK Biobank updated these data fields to address discrepancies between the original derivation and the published IPAQ guidelines, particularly regarding the handling of outliers and missing values. This update ensures consistency and accuracy in the estimation of MET scores. Further details on the derivation and updates to these fields are available at the UK Biobank resource page (https://biobank.ndph.ox.ac.uk/ukb/label.cgi?id=54).

Metabolic syndrome (MetS) scores were quantified as the total number of components meeting the criteria established by the NCEP-ATP III and IDF guidelines [11]. Five components were evaluated: (1) elevated waist circumference (≥102 cm for males; ≥88 cm for females) from Field [48-0(2).0], (2) elevated triglycerides (≥1.7 mmol/L or under triglyceride-lowering medication) from Field [30870-0(2).0], (3) reduced HDL cholesterol (<1.0 mmol/L for males; <1.3 mmol/L for females, or under HDL-raising medication) from Field [30760-0(2).0], (4) elevated blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg, or under antihypertensive treatment) from Fields [4080-0(2).0] and [4079-0(2).0], and (5) elevated fasting blood glucose (HbA1c ≥42 mmol/mol or under diabetes treatment) from Field [30740-0.0]. Each criterion met was assigned one point, producing a MetS severity score ranging from 0 (no abnormalities) to 5 (all components abnormal). MetS scores provide a comprehensive index of cumulative metabolic dysfunction, reflecting the combined impact of metabolic abnormalities on body health.

Intracranial volume (i.e. brain size), an indicator for brain size and a key covariate in neuroimaging studies, was estimated as the total brain segmentation volume estimated using FreeSurfer. Measurements were expressed in cubic millimeters (mm^3)

Region of imaging assessment center was identified based on Field [54-2.0]. Imaging visit centers were grouped into three categories: Newcastle (11027), Cheadle (11025), Reading (11026), and Bristol (11028). Our study focuses on imaging data from the first three centers (Newcastle, Cheadle, and Reading).

For missing covariate data, imputation was performed using the multiple imputation by chained equations (MICE) method [12], implemented via the random forest package in Python 3.12. To be specific, A single imputed data set was created (datasets = 1), and each conditional model within the chain was a random forest consisting of 100 trees (n_estimators = 100) with at least three observations per terminal node (min_samples_leaf = 3). All other forest settings followed the package defaults (bootstrap sampling on, unlimited depth, max_features="sqrt"). The imputation chain was iterated five times (kernel.mice(5)), after which trace plots had stabilised and the pooled potential scale-reduction factor for every variable was below 1.03, indicating satisfactory convergence. A more detailed description for missing key variables is provided in **Supplementary Table 8.**

Supplementary Tables

Supplementary Table 1. Associations between regional adiposity measures and subcortical volumes.

FD measures	Subcortical structure	Standardized β	P_{FDR}
AFP	Left Caudate	-0.048	**3.09e-07**
	Right Caudate	-0.052	**2.64e-08**
	Left Putamen	-0.006	2.64e-01
	Right Putamen	-0.024	**8.33e-03**
	Left Pallidum	-0.105	**8.58e-40**
	Right Pallidum	-0.109	**8.77e-31**
	Left Thalamus	-0.055	**2.85e-11**
	Right Thalamus	-0.066	**5.46e-15**
	Left Hippocampus	-0.082	**8.00e-20**
	Right Hippocampus	-0.083	**3.69e-21**
	Left Amygdala	-0.060	**2.86e-12**
	Right Amygdala	-0.058	**4.88e-12**
	Left Accumbens	-0.022	1.64e-02
	Right Accumbens	-0.055	**1.27e-08**
TFP	Left Caudate	-0.028	**1.74e-05**
	Right Caudate	-0.029	**5.53e-06**
	Left Putamen	0.003	6.43e-01
	Right Putamen	-0.013	3.45e-02
	Left Pallidum	-0.081	**3.41e-35**
	Right Pallidum	-0.076	**4.79e-31**
	Left Thalamus	-0.035	**6.01e-10**
	Right Thalamus	-0.038	**3.76e-11**
	Left Hippocampus	-0.054	**7.04e-18**
	Right Hippocampus	-0.053	**4.73e-18**
	Left Amygdala	-0.031	**1.29e-07**
	Right Amygdala	-0.031	**1.14e-07**
	Left Accumbens	-0.026	**1.03e-04**
	Right Accumbens	-0.035	**1.41e-07**
LFP	Left Caudate	-0.032	**6.34e-04**
	Right Caudate	-0.040	**1.55e-05**
	Left Putamen	-0.039	**6.21e-05**
	Right Putamen	-0.046	**2.15e-06**
	Left Pallidum	-0.085	**2.50e-19**
	Right Pallidum	-0.071	**7.62e-14**
	Left Thalamus	-0.047	**1.58e-08**
	Right Thalamus	-0.064	**4.14e-14**
	Left Hippocampus	-0.053	**2.56e-09**
	Right Hippocampus	-0.060	**9.24e-12**
	Left Amygdala	-0.052	**1.88e-09**

	Right Amygdala	-0.043	**2.56e-07**
	Left Accumbens	-0.025	**6.90e-03**
	Right Accumbens	-0.055	**1.15e-08**
VAT	Left Caudate	-0.015	4.30e-02
	Right Caudate	-0.009	1.47e-01
	Left Putamen	-0.016	3.81e-02
	Right Putamen	-0.020	1.14e-02
	Left Pallidum	-0.048	**5.17e-09**
	Right Pallidum	-0.055	**1.88e-11**
	Left Thalamus	-0.047	**7.64e-11**
	Right Thalamus	-0.039	**7.23e-08**
	Left Hippocampus	-0.052	**2.73e-11**
	Right Hippocampus	-0.052	**1.00e-11**
	Left Amygdala	-0.038	**3.57e-07**
	Right Amygdala	-0.026	**2.52e-04**
	Left Accumbens	-0.022	**6.30e-03**
	Right Accumbens	-0.038	**4.88e-06**

Results were adjusted for BMI and other covariates, including age at imaging visit, sex, ethnicity, handedness, years of education, employment status, smoking frequency, alcohol consumption frequency, physical activity, metabolic syndrome score, brain size, and imaging sites. P_{FDR}, false discovery rate corrected *P*. Bold values indicate *P* values corrected for FDR < 0.01.

Abbreviations: AFP, arm fat percentage; TFP, trunk fat percentage; LFP, leg fat percentage; VAT, visceral adipose tissue.

Supplementary Table 2. Mediation analysis of SMN-BAG on the relationship between regional adiposity measures and cognitive function.

Independent variable	Dependent variable (cognitive domain/cognitive test)	Number of Participants	Total effect		Direct effect		Indirect effect	
			Beta[a]	*P* value[b]	Beta[a]	*P* value[b]	Beta[a]	*P* value[b]
AFP	Reasoning/Fluid Intelligence	21,512	-0.026	3.28e-02	-0.025	4.12e-02	-0.001	1.33e-02
	Reasoning/Matrix Pattern Completion	15,369	-0.046	**1.72e-03**	-0.043	**3.16e-03**	-0.003	**1.55e-03**
	Executive Function/Tower Rearranging	15,372	-0.002	9.14e-01	-0.001	9.30e-01	0.001	5.91e-01
	Executive Function/Trail Making A	15,057	0.024	9.05e-02	0.022	1.14e-01	0.002	2.54e-02
	Executive Function/Trail Making B	15,249	0.039	**4.39e-03**	0.036	**9.11e-03**	0.003	**6.14e-04**
	Processing Speed/Symbol Digit Substitution	15,390	-0.071	**6.58e-07**	-0.068	**2.00e-06**	-0.003	**7.66e-04**
	Processing Speed/Reaction Time	21,753	0.055	**3.86e-06**	0.053	**7.06e-06**	0.002	**7.02e-03**
	Memory/Pairs Matching	21,867	-0.035	**6.96e-03**	-0.035	**6.36e-03**	0.001	2.42e-01
	Memory/Numeric Memory	15,799	-0.062	**2.40e-05**	-0.06	**3.78e-05**	-0.002	**1.46e-02**
	Memory/Paired Associate Learning	15,344	-0.048	**6.98e-04**	-0.047	**1.08e-03**	-0.002	**1.04e-02**
	Memory/Prospective Memory	15,515	0.002	7.24e-01	0.002	6.39e-01	-0.001	**1.03e-02**
TFP	Reasoning/Fluid Intelligence	21,512	-0.044	**8.16e-08**	-0.043	**1.83e-07**	-0.001	**1.34e-03**
	Reasoning/Matrix Pattern Completion	15,369	-0.034	**4.94e-04**	-0.031	**1.26e-03**	-0.003	**1.41e-04**
	Executive Function/Tower Rearranging	15,372	0.001	9.47e-01	0.001	9.25e-01	0.0002	5.85e-01
	Executive Function/Trail Making A	15,057	0.002	9.85e-01	-0.002	8.54e-01	0.002	1.18e-02
	Executive Function/Trail Making B	15,249	0.014	1.42e-01	0.011	2.66e-01	0.003	**1.51e-05**
	Processing Speed/Symbol Digit Substitution	15,390	-0.048	**7.41e-07**	-0.044	**3.67e-06**	-0.003	**1.66e-05**

	Processing Speed/Reaction Time	21,753	0.016	4.65e-02	0.015	7.67e-02	0.002	**1.55e-04**
	Memory/Pairs Matching	21,867	-0.043	**1.59e-06**	-0.043	**1.19e-06**	0.001	1.78e-01
	Memory/Numeric Memory	15,799	-0.051	**4.93e-07**	-0.05	**1.04e-06**	-0.002	**6.32e-03**
	Memory/Paired Associate Learning	15,344	-0.053	**4.16e-08**	-0.052	**1.04e-07**	-0.002	**3.96e-03**
	Memory/Prospective Memory	15,515	0.002	9.26e-01	0.0003	9.19e-01	-0.001	**4.02e-04**
LFP	Reasoning/Fluid Intelligence	21,512	-0.052	**1.42e-05**	-0.051	**2.11e-05**	-0.001	1.61e-02
	Reasoning/Matrix Pattern Completion	15,369	-0.057	**8.09e-05**	-0.055	**1.51e-04**	-0.002	**5.86e-03**
	Executive Function/Tower Rearranging	15,372	-0.005	7.44e-01	-0.005	7.57e-01	0.001	5.97e-01
	Executive Function/Trail Making A	15,057	0.034	**1.95e-02**	0.033	2.46e-02	0.001	3.85e-02
	Executive Function/Trail Making B	15,249	0.053	**2.06e-04**	0.05	**4.28e-04**	0.003	**3.21e-03**
	Processing Speed/Symbol Digit Substitution	15,390	-0.08	**1.58e-08**	-0.077	**4.53e-08**	-0.003	**3.97e-03**
	Processing Speed/Reaction Time	21,753	0.05	**3.75e-05**	0.048	**6.22e-05**	0.001	1.11e-02
	Memory/Pairs Matching	21,867	-0.028	3.11e-02	-0.028	2.90e-02	0.0001	2.51e-01
	Memory/Numeric Memory	15,799	-0.056	**1.09e-04**	-0.055	**1.55e-04**	-0.001	2.74e-02
	Memory/Paired Associate Learning	15,344	-0.065	**4.63e-06**	-0.063	**7.37e-06**	-0.001	2.21e-02
	Memory/Prospective Memory	15,515	-0.002	6.46e-01	-0.002	7.22e-01	0.0001	1.50e-02
VAT	Reasoning/Fluid Intelligence	21,512	-0.04	**2.36e-05**	-0.037	**8.82e-05**	-0.003	**2.23e-04**
	Reasoning/Matrix Pattern Completion	15,369	-0.034	**3.08e-03**	-0.028	1.29e-02	-0.006	**4.04e-06**
	Executive Function/Tower Rearranging	15,372	0.0001	9.92e-01	0.001	9.66e-01	-0.001	5.85e-01
	Executive Function/Trail Making A	15,057	-0.007	5.72e-01	-0.01	3.80e-01	0.004	**5.88e-03**
	Executive Function/Trail Making B	15,249	0.006	5.65e-01	-0.001	9.13e-01	0.007	**4.87e-08**

Processing Speed/Symbol Digit Substitution	15,390	-0.067	**1.28e-09**	-0.06	**3.85e-08**	-0.007	**4.46e-08**
Processing Speed/Reaction Time	21,753	0.007	4.76e-01	0.002	8.11e-01	0.005	**8.62e-07**
Memory/Pairs Matching	21,867	-0.053	**1.10e-07**	-0.054	**4.35e-08**	0.001	1.03e-01
Memory/Numeric Memory	15,799	-0.048	**7.16e-05**	-0.045	**2.04e-04**	-0.003	**3.75e-03**
Memory/Paired Associate Learning	15,344	-0.057	**1.22e-06**	-0.053	**4.84e-06**	-0.004	**2.15e-03**
Memory/Prospective Memory	15,515	0.001	8.61e-01	0.002	5.52e-01	-0.001	**9.84e-06**

[a] standardized beta coefficient

[b] *P* values were derived from mediation analysis using two-sided significance testing. False discovery rate (FDR) correction was applied to adjust for multiple comparisons of *P* values. Bold values indicate *P* values corrected for FDR < 0.01.

Abbreviations: SMN-BAG: brain age gap derived from the sensorimotor system; AFP, arm fat percentage; TFP, trunk fat percentage; LFP, leg fat percentage; VAT, visceral adipose tissue.

Supplementary Table 3. Mediation analysis of DMN-BAG on the relationship between regional adiposity measures and cognitive function.

Independent variable	Dependent variable (cognitive domain/cognitive test)	Number of Participants	Total effect		Direct effect		Indirect effect	
			Beta[a]	*P* value[b]	Beta[a]	*P* value[b]	Beta[a]	*P* value[b]
AFP	Reasoning/Fluid Intelligence	21,512	-0.026	3.28e-02	-0.023	5.46e-02	-0.003	**1.42e-04**
	Reasoning/Matrix Pattern Completion	15,369	-0.046	**1.73e-03**	-0.043	**3.35e-03**	-0.003	**1.30e-03**
	Executive Function/Tower Rearranging	15,372	-0.002	9.15e-01	0.0001	9.94e-01	-0.002	4.34e-02
	Executive Function/Trail Making A	15,057	0.024	9.07e-02	0.020	1.52e-01	0.004	**4.17e-04**
	Executive Function/Trail Making B	15,249	0.039	**4.57e-03**	0.034	1.45e-02	0.006	**7.34e-06**
	Processing Speed/Symbol Digit Substitution	15,390	-0.071	**6.64e-07**	-0.065	**4.45e-06**	-0.006	**2.53e-06**
	Processing Speed/Reaction Time	21,753	0.055	**4.06e-06**	0.052	**1.25e-05**	0.003	**5.08e-05**
	Memory/Pairs Matching	21,867	-0.035	**7.04e-03**	-0.036	**5.10e-03**	0.001	3.40e-02
	Memory/Numeric Memory	15,799	-0.062	**2.44e-05**	-0.061	**3.52e-05**	-0.001	1.02e-01
	Memory/Paired Associate Learning	15,344	-0.048	**7.08e-04**	-0.045	**1.65e-03**	-0.004	**3.67e-04**
	Memory/Prospective Memory	15,515	0.002	7.24e-01	0.003	5.35e-01	-0.001	**3.61e-05**
TFP	Reasoning/Fluid Intelligence	21,512	-0.044	**8.27e-08**	-0.042	**3.05e-07**	-0.002	**7.25e-05**
	Reasoning/Matrix Pattern Completion	15,369	-0.034	**4.96e-04**	-0.031	**1.17e-03**	-0.002	**8.91e-04**
	Executive Function/Tower Rearranging	15,372	0.001	9.47e-01	0.002	8.37e-01	-0.001	3.88e-02
	Executive Function/Trail Making A	15,057	0.0001	9.85e-01	-0.003	7.38e-01	0.003	**1.41e-04**
	Executive Function/Trail Making B	15,249	0.014	1.43e-01	0.009	3.26e-01	0.005	**6.38e-07**
	Processing Speed/Symbol Digit Substitution	15,390	-0.048	**7.63e-07**	-0.043	**7.74e-06**	-0.005	**1.51e-07**
	Processing Speed/Reaction Time	21,753	0.016	4.70e-02	0.014	9.12e-02	0.002	**1.04e-05**

	Memory/Pairs Matching	21,867	-0.043	**1.59e-06**	-0.044	**7.95e-07**	0.001	2.20e-02
	Memory/Numeric Memory	15,799	-0.051	**5.15e-07**	-0.05	**8.19e-07**	-0.001	1.18e-01
	Memory/Paired Associate Learning	15,344	-0.053	**4.33e-08**	-0.051	**1.95e-07**	-0.003	**2.34e-04**
	Memory/Prospective Memory	15,515	0.0001	9.27e-01	0.001	8.22e-01	-0.001	**8.05e-06**
LFP	Reasoning/Fluid Intelligence	21,512	-0.052	**1.42e-05**	-0.049	**3.45e-05**	-0.002	**2.13e-04**
	Reasoning/Matrix Pattern Completion	15,369	-0.057	**8.23e-05**	-0.054	**1.75e-04**	-0.003	1.71e-03
	Executive Function/Tower Rearranging	15,372	-0.005	7.44e-01	-0.003	8.28e-01	-0.002	4.59e-02
	Executive Function/Trail Making A	15,057	0.034	1.95e-02	0.031	3.53e-02	0.003	**6.05e-04**
	Executive Function/Trail Making B	15,249	0.053	**2.16e-04**	0.048	**7.97e-04**	0.005	**1.78e-05**
	Processing Speed/Symbol Digit Substitution	15,390	-0.08	**1.72e-08**	-0.075	**1.31e-07**	-0.005	**7.20e-06**
	Processing Speed/Reaction Time	21,753	0.05	**3.91e-05**	0.047	**1.03e-04**	0.003	**6.98e-05**
	Memory/Pairs Matching	21,867	-0.028	3.14e-02	-0.029	2.44e-02	0.001	3.73e-02
	Memory/Numeric Memory	15,799	-0.056	**1.12e-04**	-0.055	**1.55e-04**	-0.001	9.69e-02
	Memory/Paired Associate Learning	15,344	-0.065	**4.88e-06**	-0.061	**1.35e-05**	-0.003	**5.69e-04**
	Memory/Prospective Memory	15,515	-0.002	6.47e-01	-0.001	8.28e-01	-0.001	**6.34e-05**
VAT	Reasoning/Fluid Intelligence	21,512	-0.04	**2.45e-05**	-0.036	**1.35e-04**	-0.004	**1.66e-05**
	Reasoning/Matrix Pattern Completion	15,369	-0.034	3.06e-03	-0.03	**9.33e-03**	-0.004	**4.96e-04**
	Executive Function/Tower Rearranging	15,372	0.0001	9.92e-01	0.003	8.31e-01	-0.003	3.41e-02
	Executive Function/Trail Making A	15,057	-0.007	5.73e-01	-0.013	2.85e-01	0.006	**2.49e-05**
	Executive Function/Trail Making B	15,249	0.006	5.66e-01	-0.002	8.18e-01	0.009	**5.37e-09**
	Processing Speed/Symbol Digit Substitution	15,390	-0.067	**1.15e-09**	-0.059	**8.60e-08**	-0.009	**3.35e-10**

Processing Speed/Reaction Time	21,753	0.007	4.76e-01	0.002	8.43e-01	0.005	**3.07e-07**
Memory/Pairs Matching	21,867	-0.053	**1.06e-07**	-0.055	**2.16e-08**	0.003	**9.71e-03**
Memory/Numeric Memory	15,799	-0.048	**7.45e-05**	-0.046	**1.27e-04**	-0.002	1.35e-01
Memory/Paired Associate Learning	15,344	-0.057	**1.32e-06**	-0.052	**9.41e-06**	-0.005	**9.69e-05**
Memory/Prospective Memory	15,515	0.001	8.62e-01	0.003	4.74e-01	-0.002	**2.51e-07**

[a] standardized beta coefficient

[b] *P* values were derived from mediation analysis using two-sided significance testing. False discovery rate (FDR) correction was applied to adjust for multiple comparisons of *P* values. Bold values indicate *P* values corrected for FDR < 0.01.

Abbreviations: DMN-BAG: brain age gap derived from the default mode system; AFP, arm fat percentage; TFP, trunk fat percentage; LFP, leg fat percentage; VAT, visceral adipose tissue.

Supplementary Table 4. Mediation analysis of LIM-BAG on the relationship between regional adiposity measures and cognitive function.

Independent variable	Dependent variable (cognitive domain/cognitive test)	Number of Participants	Total effect		Direct effect		Indirect effect	
			Beta[a]	*P* value[b]	Beta[a]	*P* value[b]	Beta[a]	*P* value[b]
AFP	Reasoning/Fluid Intelligence	21,512	-0.026	3.29e-02	-0.023	5.17e-02	-0.002	**8.62e-04**
	Reasoning/Matrix Pattern Completion	15,369	-0.046	**1.75e-03**	-0.042	3.62e-03	-0.003	**8.88e-04**
	Executive Function/Tower Rearranging	15,372	-0.002	9.14e-01	0.0001	9.90e-01	-0.002	4.64e-02
	Executive Function/Trail Making A	15,057	0.024	9.11e-02	0.018	1.84e-01	0.005	**1.48e-04**
	Executive Function/Trail Making B	15,249	0.039	**4.65e-03**	0.033	1.65e-02	0.006	**8.45e-06**
	Processing Speed/Symbol Digit Substitution	15,390	-0.071	**6.50e-07**	-0.067	2.64e-06	-0.004	**5.79e-05**
	Processing Speed/Reaction Time	21,753	0.055	**4.00e-06**	0.052	1.18e-05	0.003	**1.83e-04**
	Memory/Pairs Matching	21,512	-0.035	**7.03e-03**	-0.037	4.32e-03	0.002	**5.46e-03**
	Memory/Numeric Memory	15,369	-0.062	**2.45e-05**	-0.062	2.41e-05	0.0001	9.55e-01
	Memory/Paired Associate Learning	15,372	-0.048	**7.22e-04**	-0.045	1.64e-03	-0.003	**6.65e-04**
	Memory/Prospective Memory	15,057	0.002	7.25e-01	0.003	5.25e-01	-0.001	**3.33e-05**
TFP	Reasoning/Fluid Intelligence	21,512	-0.044	**8.27e-08**	-0.043	**2.35e-07**	-0.002	**9.22e-04**
	Reasoning/Matrix Pattern Completion	15,369	-0.034	**5.03e-04**	-0.031	**1.20e-03**	-0.002	**7.55e-04**
	Executive Function/Tower Rearranging	15,372	0.001	9.47e-01	0.002	8.42e-01	-0.001	4.34e-02
	Executive Function/Trail Making A	15,057	0.0001	9.85e-01	-0.004	6.80e-01	0.004	**7.91e-05**
	Executive Function/Trail Making B	15,249	0.014	1.44e-01	0.009	3.24e-01	0.005	**2.99e-06**
	Processing Speed/Symbol Digit Substitution	15,390	-0.048	**7.37e-07**	-0.044	**3.43e-06**	-0.003	**3.22e-05**

	Processing Speed/Reaction Time	21,753	0.016	4.68e-02	0.014	8.45e-02	0.002	**9.28e-05**
	Memory/Pairs Matching	21,512	-0.043	**1.66e-06**	-0.044	**6.63e-07**	0.002	**3.43e-03**
	Memory/Numeric Memory	15,369	-0.051	**5.18e-07**	-0.051	**4.89e-07**	0.0001	9.82e-01
	Memory/Paired Associate Learning	15,372	-0.053	**4.52e-08**	-0.051	**1.69e-07**	-0.002	**6.55e-04**
	Memory/Prospective Memory	15,057	0.0001	9.27e-01	0.001	8.31e-01	-0.001	**2.00e-05**
LFP	Reasoning/Fluid Intelligence	21,512	-0.052	**1.42e-05**	-0.05	**2.85e-05**	-0.002	**1.74e-03**
	Reasoning/Matrix Pattern Completion	15,369	-0.057	**8.15e-05**	-0.055	**1.52e-04**	-0.002	**3.29e-03**
	Executive Function/Tower Rearranging	15,372	-0.005	7.44e-01	-0.004	8.09e-01	-0.001	5.83e-02
	Executive Function/Trail Making A	15,057	0.034	2.01e-02	0.031	3.61e-02	0.003	**1.43e-03**
	Executive Function/Trail Making B	15,249	0.053	**2.03e-04**	0.049	**5.93e-04**	0.004	**3.66e-04**
	Processing Speed/Symbol Digit Substitution	15,390	-0.08	**1.55e-08**	-0.077	**4.70e-08**	-0.003	**8.88e-04**
	Processing Speed/Reaction Time	21,753	0.05	**3.72e-05**	0.047	**8.78e-05**	0.003	**3.35e-04**
	Memory/Pairs Matching	21,512	-0.028	3.14e-02	-0.03	2.22e-02	0.002	**7.57e-03**
	Memory/Numeric Memory	15,369	-0.056	**1.11e-04**	-0.056	**1.12e-04**	0.0001	8.79e-01
	Memory/Paired Associate Learning	15,372	-0.065	**4.73e-06**	-0.062	**9.88e-06**	-0.002	**3.72e-03**
	Memory/Prospective Memory	15,057	-0.002	6.47e-01	-0.001	8.24e-01	-0.001	**1.15e-04**
VAT	Reasoning/Fluid Intelligence	21,512	-0.04	**2.32e-05**	-0.038	**8.07e-05**	-0.003	**5.01e-04**
	Reasoning/Matrix Pattern Completion	15,369	-0.034	**2.98e-03**	-0.03	**7.87e-03**	-0.004	**4.85e-04**
	Executive Function/Tower Rearranging	15,372	0.0001	9.92e-01	0.002	8.68e-01	-0.002	4.05e-02
	Executive Function/Trail Making A	15,057	-0.007	5.76e-01	-0.013	2.78e-01	0.006	**2.17e-05**
	Executive Function/Trail Making B	15,249	0.006	5.65e-01	-0.001	9.20e-01	0.007	**2.11e-07**
	Processing Speed/Symbol Digit Substitution	15,390	-0.067	**1.02e-09**	-0.063	**1.12e-08**	-0.005	**1.18e-05**

Processing Speed/Reaction Time	21,753	0.007	4.75e-01	0.003	7.53e-01	0.004	**1.78e-05**
Memory/Pairs Matching	21,512	-0.053	**1.03e-07**	-0.055	**1.73e-08**	0.003	**1.34e-03**
Memory/Numeric Memory	15,369	-0.048	**6.81e-05**	-0.048	**6.28e-05**	0.0001	9.51e-01
Memory/Paired Associate Learning	15,372	-0.057	**1.19e-06**	-0.053	**5.41e-06**	-0.004	**3.68e-04**
Memory/Prospective Memory	15,057	0.001	8.62e-01	0.002	5.25e-01	-0.002	**2.40e-06**

[a] standardized beta coefficient

[b] *P* values were derived from mediation analysis using two-sided significance testing. False discovery rate (FDR) correction was applied to adjust for multiple comparisons of *P* values. Bold values indicate *P* values corrected for FDR < 0.01.

Abbreviations: LIM-BAG: brain age gap derived from the limbic system; AFP, arm fat percentage; TFP, trunk fat percentage; LFP, leg fat percentage; VAT, visceral adipose tissue.

Supplementary Table 5. Mediation analysis of SUB-CEB-BST-BAG on the relationship between regional adiposity measures and cognitive function.

Independent variable	Dependent variable (cognitive domain/cognitive test)	Number of Participants	Total effect		Direct effect		Indirect effect	
			Beta[a]	*P* value[b]	Beta[a]	*P* value[b]	Beta[a]	*P* value[b]
AFP	Reasoning/Fluid Intelligence	21,512	-0.027	2.72e-02	-0.027	**2.75e-02**	4.21e-05	6.35e-01
	Reasoning/Matrix Pattern Completion	15,369	-0.045	**1.61e-03**	-0.045	**1.66e-03**	1.16e-04	6.62e-01
	Executive Function/Tower Rearranging	15,372	-0.002	9.02e-01	-0.002	9.00e-01	1.43e-06	7.51e-01
	Executive Function/Trail Making A	15,057	0.024	9.59e-02	0.024	9.73e-02	-7.10e-05	6.11e-01
	Executive Function/Trail Making B	15,249	0.040	**3.95e-03**	0.040	**4.01e-03**	-5.62e-05	6.59e-01
	Processing Speed/Symbol Digit Substitution	15,390	-0.071	**3.47e-07**	-0.071	**3.56e-07**	1.36e-04	6.76e-01
	Processing Speed/Reaction Time	21,753	0.055	**7.30e-06**	0.055	**6.70e-06**	-2.35e-04	3.30e-01
	Memory/Pairs Matching	21,512	-0.034	**7.37e-03**	-0.034	**7.67e-03**	-1.44e-04	4.03e-01
	Memory/Numeric Memory	15,369	-0.062	**3.40e-05**	-0.062	**3.41e-05**	1.23e-06	7.87e-01
	Memory/Paired Associate Learning	15,372	-0.049	**7.08e-04**	-0.049	**7.31e-04**	1.10e-04	6.19e-01
	Memory/Prospective Memory	15,057	0.001	7.47e-01	0.001	7.47e-01	7.62e-05	8.94e-01
TFP	Reasoning/Fluid Intelligence	21,512	-0.045	**4.03e-08**	-0.045	**4.17e-08**	3.92e-05	6.20e-01
	Reasoning/Matrix Pattern Completion	15,369	-0.034	**5.20e-04**	-0.034	**4.97e-04**	1.75e-04	5.82e-01
	Executive Function/Tower Rearranging	15,372	0.001	9.51e-01	0.001	9.47e-01	1.70e-06	6.35e-01
	Executive Function/Trail Making A	15,057	0.0002	9.80e-01	0.0001	9.86e-01	-1.04e-04	6.48e-01

	Executive Function/Trail Making B	15,249	0.014	1.38e-01	0.014	1.37e-01	-1.10e-04	7.03e-01
	Processing Speed/Symbol Digit Substitution	15,390	-0.048	**3.32e-07**	-0.048	**3.17e-07**	2.21e-04	5.86e-01
	Processing Speed/Reaction Time	21,753	0.016	5.27e-02	0.016	4.94e-02	-2.26e-04	1.86e-01
	Memory/Pairs Matching	21,512	-0.043	**1.11e-06**	-0.043	**1.23e-06**	-1.37e-04	2.24e-01
	Memory/Numeric Memory	15,369	-0.051	**6.55e-07**	-0.051	**6.48e-07**	4.30e-06	7.48e-01
	Memory/Paired Associate Learning	15,372	-0.054	**7.09e-08**	-0.054	**6.70e-08**	1.58e-04	6.16e-01
	Memory/Prospective Memory	15,057	0.0002	9.37e-01	0.0003	9.38e-01	7.35e-05	8.96e-01
LFP	Reasoning/Fluid Intelligence	21,512	-0.053	**1.10e-05**	-0.053	**1.12e-05**	9.11e-06	6.45e-01
	Reasoning/Matrix Pattern Completion	15,369	-0.057	**8.44e-05**	-0.056	**8.42e-05**	-1.39e-04	9.85e-01
	Executive Function/Tower Rearranging	15,372	-0.005	7.36e-01	-0.005	7.37e-01	-1.69e-06	9.33e-01
	Executive Function/Trail Making A	15,057	0.035	**2.10e-02**	0.034	**2.11e-02**	8.81e-05	8.90e-01
	Executive Function/Trail Making B	15,249	0.054	**2.11e-04**	0.053	**2.12e-04**	1.75e-04	9.10e-01
	Processing Speed/Symbol Digit Substitution	15,390	-0.080	**1.12e-08**	-0.080	**1.12e-08**	-2.07e-04	9.97e-01
	Processing Speed/Reaction Time	21,753	0.050	**7.16e-05**	0.050	**6.76e-05**	1.62e-05	4.38e-01
	Memory/Pairs Matching	21,512	-0.027	**3.39e-02**	-0.027	**3.48e-02**	1.07e-05	4.82e-01
	Memory/Numeric Memory	15,369	-0.056	**1.35e-04**	-0.056	**1.35e-04**	-4.94e-06	9.71e-01
	Memory/Paired Associate Learning	15,372	-0.065	**5.30e-06**	-0.065	**5.32e-06**	-9.97e-05	9.35e-01
	Memory/Prospective Memory	15,057	-0.002	6.35e-01	-0.002	6.35e-01	-4.74e-06	8.98e-01
VAT	Reasoning/Fluid Intelligence	21,512	-0.040	**1.87e-05**	-0.040	**1.85e-05**	-7.80e-05	6.76e-01

Reasoning/Matrix Pattern Completion	15,369	-0.034	**2.39e-03**	-0.033	**2.55e-03**	-7.55e-04	3.65e-01
Executive Function/Tower Rearranging	15,372	0.000	9.87e-01	0.000	9.92e-01	-1.04e-05	5.41e-01
Executive Function/Trail Making A	15,057	-0.007	5.67e-01	-0.007	5.58e-01	5.35e-04	4.40e-01
Executive Function/Trail Making B	15,249	0.006	5.65e-01	0.005	5.71e-01	7.77e-04	5.07e-01
Processing Speed/Symbol Digit Substitution	15,390	-0.068	**2.69e-10**	-0.067	**2.91e-10**	-9.88e-04	4.26e-01
Processing Speed/Reaction Time	21,753	0.007	4.65e-01	0.006	4.70e-01	6.92e-04	6.50e-01
Memory/Pairs Matching	21,512	-0.052	**7.30e-08**	-0.053	**6.91e-08**	4.59e-04	5.76e-01
Memory/Numeric Memory	15,369	-0.048	**6.42e-05**	-0.048	**6.50e-05**	3.39e-06	7.34e-01
Memory/Paired Associate Learning	15,372	-0.057	**7.13e-07**	-0.056	**7.82e-07**	-6.78e-04	3.53e-01
Memory/Prospective Memory	15,057	0.001	8.53e-01	0.001	8.53e-01	-2.40e-04	8.98e-01

[a] standardized beta coefficient

[b] *P* values were derived from mediation analysis using two-sided significance testing. False discovery rate (FDR) correction was applied to adjust for multiple comparisons of *P* values. Bold values indicate *P* values corrected for FDR < 0.01.

Abbreviations: SUB-CEB-BST-BAG: brain age gap derived from the subcortical-cerebellar-brainstem system; AFP, arm fat percentage; TFP, trunk fat percentage; LFP, leg fat percentage; VAT, visceral adipose tissue.

Supplementary Table 6. Cognitive tests.

Cognitive domain	Test name	Description	Scoring
Reasoning	Fluid Intelligence Test	Participants are presented with 13 multiple-choice questions assessing verbal and numerical reasoning abilities. Each question appears at the top of the screen with 3–5 possible answers listed below. Participants select the correct answer or choose "Do not know" or "Prefer not to answer." They have 2 minutes to solve as many problems as possible. Unanswered or incorrect questions are scored as zero.	Total number of correct answers (max score: 13).
	Matrix Pattern Test	Participants were shown a series of visual patterns with one missing element. They were required to identify the correct missing element from a set of options. This task evaluated nonverbal reasoning and problem-solving skills.	Number of correctly identified missing elements.
Executive Function	Trail Making Test	The test was divided into two parts: **Part A**: Participants connected a sequence of numbered circles as quickly as possible, assessing attention and visual-motor tracking. **Part B**: Participants connected circles following an alternating alphanumeric sequence (e.g., 1-A-2-B) to evaluate cognitive flexibility and attention.	Completion time recorded in deciseconds for each part.
	Tower Rearranging Test	Participants were required to rearrange blocks under specific constraints to evaluate planning and problem-solving skills. Tasks involved completing puzzles with increasing complexity.	Number of puzzles correctly solved.

Processing Speed	Symbol Digit Substitution Test	Participants were presented with a reference table pairing symbols with numbers and a separate table containing only symbols. They were tasked to match as many symbols to their corresponding numbers as possible within a limited time.	Number of correct matches within the time limit.
	Reaction Time Test	Participants responded to visual stimuli by pressing a button as quickly as possible. This task consisted of nine trials, measuring motor response speed.	Mean reaction time across all nine trials (in milliseconds).
Memory	Pairs Matching Test	Participants were shown a grid of card pairs that were briefly displayed and then flipped over. They were tasked to recall and match pairs of cards from memory.	Total number of correctly matched card pairs.
	Numeric Memory Test	Participants were required to recall sequences of numbers that increased in length with each successful attempt. This task assessed short-term memory capacity.	Maximum sequence length correctly recalled.
	Paired Associate Learning Test	Participants learned a set of item pairs (e.g., words or images) during an initial phase. They were then tasked to recall the correct pairs after a delay.	Number of correctly recalled pairs.
	Prospective Memory Test	Participants were instructed to remember to perform a specific action (e.g., press a button or select a shape) after a delay during other ongoing tasks. The test evaluated prospective memory and delayed recall abilities.	Binary outcome: Success (correctly performed action) or failure.

Supplementary Table 7. Summary of MRI quality control exclusions across imaging modalities

QC reasons	T1-weighted	rsfMRI	dMRI (NODDI model)
QC criterion 1	Severe motion, severe bias-field, incomplete brain coverage, or other acquisition artefact (e.g. metal artifacts, aliasing (fold-over) artifacts, and reconstruction artifacts) **N=1 492/n=1 104**	High motion (FD > 0.5 mm or more than 20 volumes exceeding a head motion threshold of 0.1 mm) **N=1 142/n=811**	Gradient-dropout, TOPUP/EDDY failure, gross susceptibility artefact **N=213/n=133**
QC criterion 2	Visual inspection revealed skull-strip errors, pervasive sulcal over- or under-segmentation, or large cortical misclassification **N=1 133/n=1 031**	Residual ghosting / spikes **N=336/n=276**	> 5 % outlier-replaced slices or mean residual > 0.5 **N=233/n=147**
QC criterion 3	—	Failed fMRI to T1 registration **N=379/n=298**	> 10 % WM voxels with unphysical NDI/ODI **N=276/n=149**

Uppercase "N" denotes the number of participants with AFP, TFP, and LFP measurements, while lowercase "n" denotes the number of participants with VAT measurements. "—" indicates data not available for that modality.

Abbreviations: QC, quality control; rsfMRI, resting-state functional MRI; dMRI, diffusion MRI; NODDI, neurite orientation dispersion and density imaging; WM, whiter matter; FD, framewise displacement; NDI, neurite density index; ODI, orientation dispersion index.

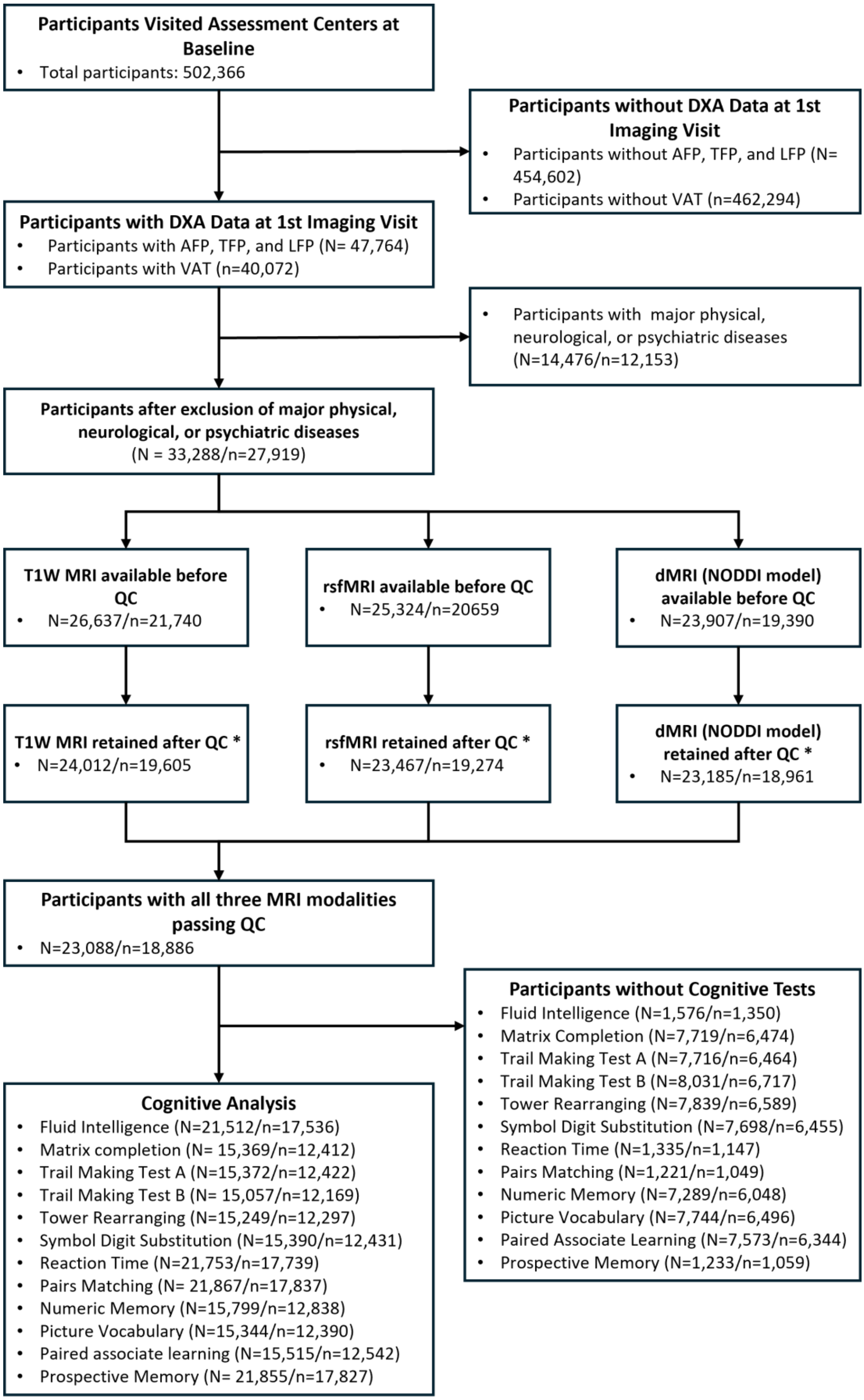
Supplementary Table 8. Missingness of covariates.

covariates	Participants with AFP/TFP/LFP (N=23,088)	Participants with VAT (n=18,886)
Physical activity frequency	3403(14.74%)	2815(14.90%)
Alcohol consumption frequency	1(0.04%)	1(0.05%)
Smoking frequency	20(0.86%)	18(0.95%)
Ethnicity	5(0.21%)	5(0.26%)

Uppercase “N” denotes the number of participants with AFP, TFP, and LFP measurements, while lowercase “n” denotes the number of participants with VAT measurements.

Abbreviations: AFP, arm fat percentage; TFP, trunk fat percentage; LFP, leg fat percentage; VAT, visceral adipose tissue.

Supplementary Figures

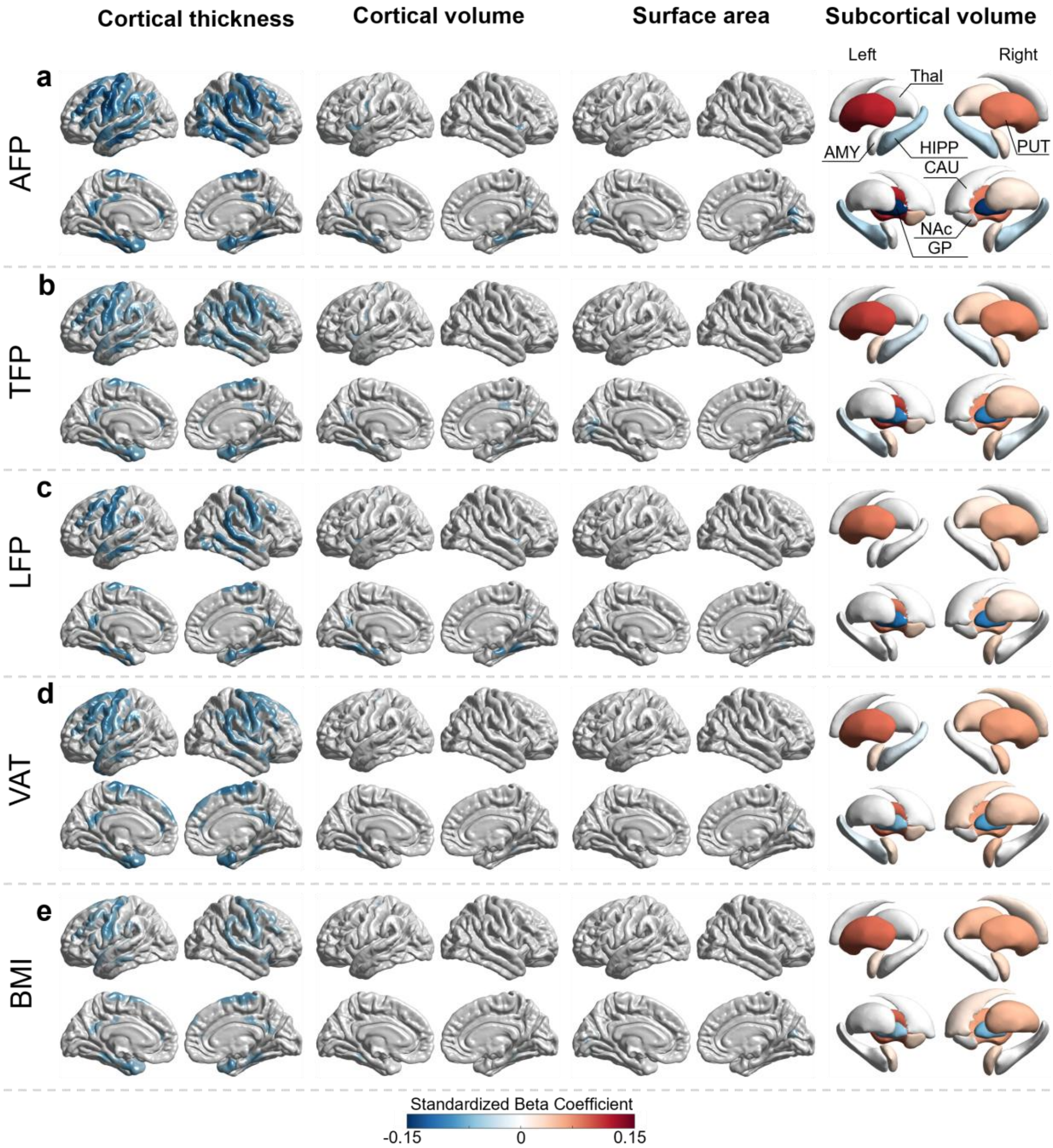


Supplementary Fig. 1. Flowchart of the participant selection.

Uppercase “N” denotes the number of participants with AFP, TFP, and LFP measurements, while lowercase “n” denotes the number of participants with VAT measurements.

* indicates imaging data retained after quality control; detailed modality-specific criteria and reasons for MRI data exclusion are presented in **Supplementary Table 7** and elaborated in the **MRI Quality Control** section of the Supplementary Methods.

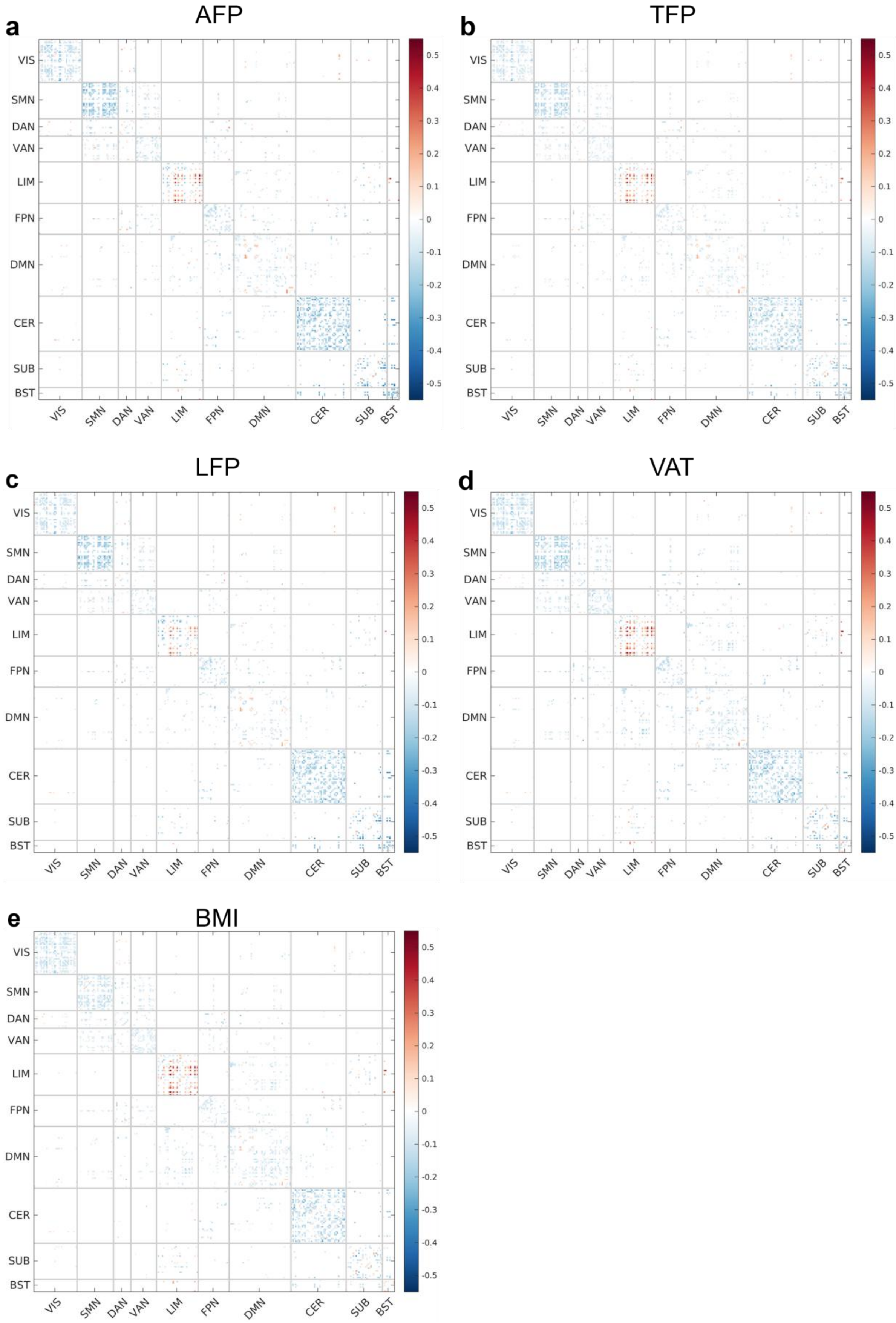
Abbreviations: AFP, arm fat percentage; TFP, trunk fat percentage; LFP, leg fat percentage; VAT, visceral adipose tissue; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; T1W, T1-weighted; rsfMRI, resting-state functional MRI; dMRI, diffusion MRI; NODDI, neurite orientation dispersion and density imaging.



Supplementary Fig. 2. Associations of regional adiposity and BMI with raw (unadjusted) cortical and subcortical morphometry.

Panels **a-d** represent the associations between raw (unadjusted) regional adiposity measures and brain morphology, with each column corresponding to a morphological parameter: cortical thickness, cortical volume, surface area, and subcortical volume (from left to right). Panel **e** represents the relationship between BMI and the same morphological parameters. The color bar represents standardized beta coefficients, with cooler colors (blue) indicating negative correlations. One-sided linear models were used to examine these associations, and all models were adjusted covariates, including age at imaging visit, sex, ethnicity, handedness, years of education, employment status, smoking frequency, alcohol consumption frequency, physical activity, metabolic syndrome score, brain size, and imaging sites. For cortical morphological analysis, random field theory was applied to correct for multiple comparisons at a vertex-level threshold of $P < 0.001$ and a cluster-level threshold of $P < 0.01$. False discovery rate was used to correct for multiple comparisons among subcortical volumes at a threshold of $P < 0.01$.

Abbreviations: AFP, arm fat percentage; TFP, trunk fat percentage; LFP, leg fat percentage; VAT, visceral adipose tissue; BMI, body mass index; AMY, amygdala; CAU, caudate; HIPP, hippocampus; GP, globus pallidus; NAc, nucleus accumbens; PUT, putamen; Thal, thalamus.

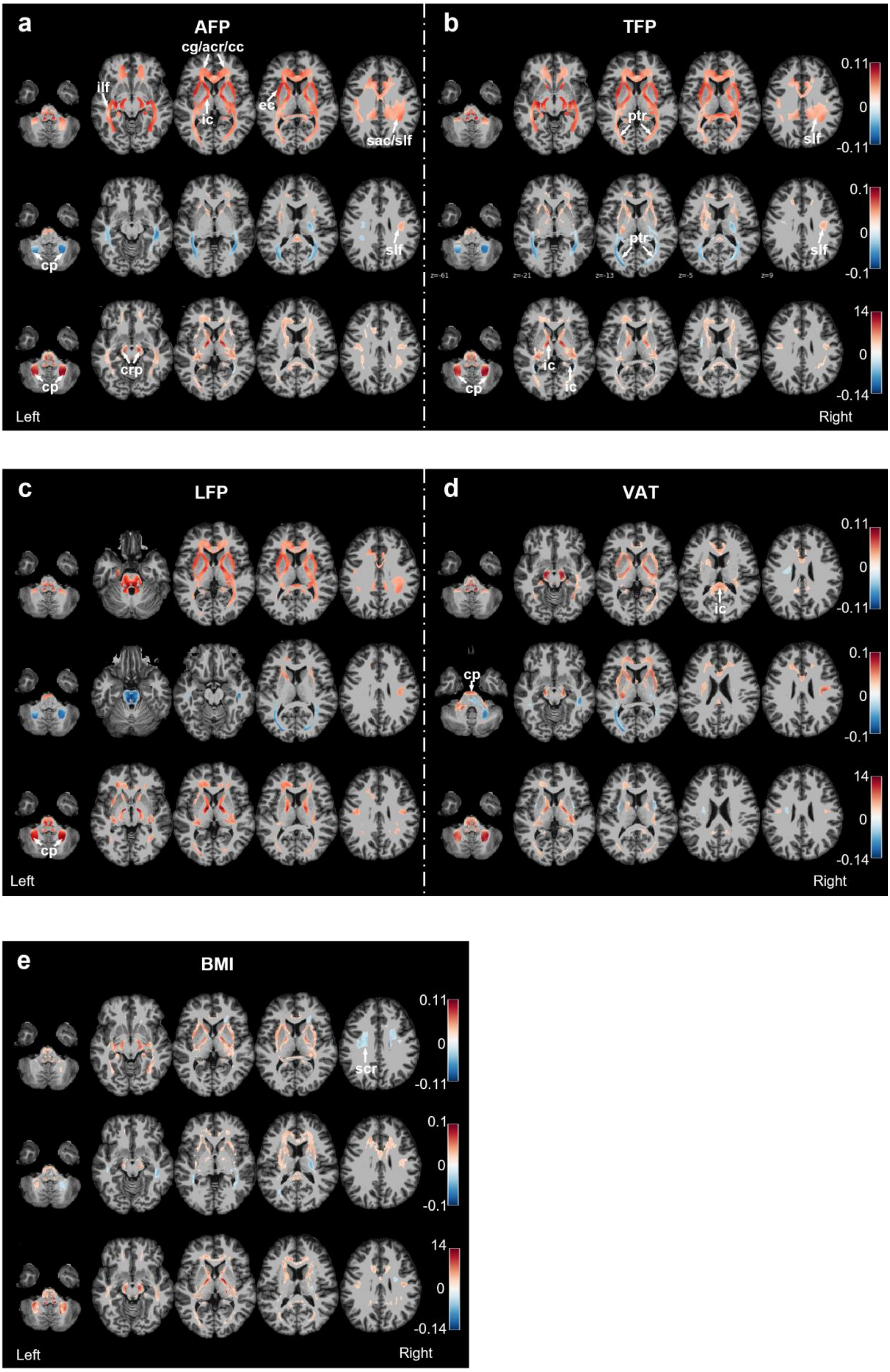


a
AFP
b
TFP
c
LFP
d
VAT
e
BMI
VIS
SMN
DAN
VAN
LIM
FPN
DMN
CER
SUB
BST
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5

Supplementary Fig. 3. Associations of regional adiposity and BMI with raw (unadjusted) functional connectivity.

Panels **a-d** represent the associations between raw (unadjusted) regional adiposity measures and functional connectivity, while panel **e** represents the associations between BMI and functional connectivity. Significant connections and their corresponding subnetworks are displayed. The color bar represents standardized beta coefficients, with warmer colors (red) indicating positive correlations and cooler colors (blue) indicating negative correlations.
Two-sided linear models were used to examine these associations, and all models were adjusted for covariates, including age at imaging visit, sex, ethnicity, handedness, years of education, employment status, smoking frequency, alcohol consumption frequency, physical activity, metabolic syndrome score, brain size, and imaging sites. False discovery rate correction was applied with threshold of $P < 0.01$.

Abbreviations: AFP, arm fat percentage; TFP, trunk fat percentage; LFP, leg fat percentage; VAT, visceral adipose tissue; BMI, body mass index; VIS, visual network; SMN, somatomotor network; DAN, dorsal attention network; VAN, ventral attention network; LIM, limbic network; FPN, frontoparietal network; DMN, default mode network; CER, cerebellar network; SUB, subcortical network; BST, brainstem network.

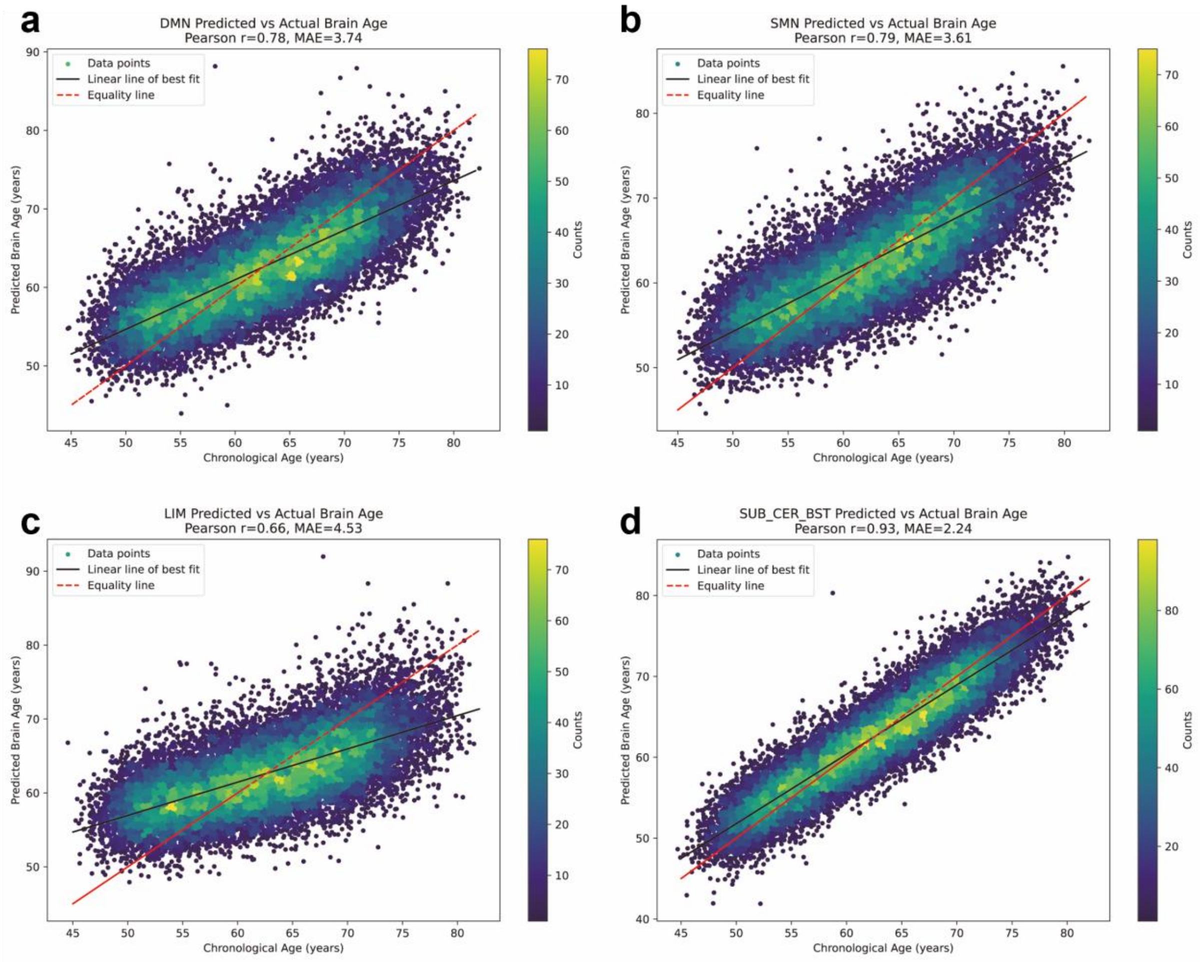


a
AFP
b
TFP
NDI
ISOVF
ODI
cg/acr/cc
ilf
ic
ec
sac/slf
ptr
slf
cp
crp
0.11
0
-0.11
0.1
-0.1
14
-0.14
Left
Right
c
LFP
d
VAT
e
BMI
scr

Supplementary Fig. 4. Associations of regional adiposity and BMI with raw (unadjusted) NODDI metrics.

Panels **a–d** represent the associations between raw (unadjusted) regional adiposity measures and three NODDI metrics: NDI, ISOVF and ODI. Panel **e** displays the associations between BMI and the same NODDI metrics. Regions with significant associations are highlighted, with warm colors (red) indicating positive correlations and cool colors (blue) indicating negative correlations, represented by standardized beta coefficients. Two-sided linear models were used to examine these associations, and all models were adjusted for covariates, including age at imaging visit, sex, ethnicity, handedness, years of education, employment status, smoking frequency, alcohol consumption frequency, physical activity, metabolic syndrome score, brain size, and imaging sites. Statistical significance was determined using random field theory correction with a voxel-level threshold of $P < 0.001$ and a cluster-level threshold of $P < 0.01$.

Abbreviations: AFP, arm fat percentage; TFP, trunk fat percentage; LFP, leg fat percentage; VAT, visceral adipose tissue ; BMI, body mass index; NDI, neurite density index; ISOVF, isotropic volume fraction; ODI, orientation dispersion index; NODDI, neurite orientation dispersion and density imaging; slf, superior longitudinal fasciculus; ilf, inferior longitudinal fasciculus; ptr, posterior thalamic radiation; arc, anterior corona radiata; src, superior corona radiata; cg, cingulum; cc, corpus callosum; ec, external capsule; ic, internal capsule; hipp, hippocampus; cp, cerebellar peduncle; crp, cerebral peduncle.



Supplementary Fig. 5. Performance of the multimodal brain age prediction model. a-d Prediction of brain age using 10-fold cross-validation based on multimodal brain imaging data. The mean absolute error (MAE) and Pearson correlation coefficient between predicted brain age (years) and chronological age (years) are shown in the top panel.

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