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Abstract

Unraveling the heterogeneity of autism spectrum disorder (ASD) remains a major challenge yet crucial for elucidating the etiological underpinnings. Leveraging large-scale MRI data from 60,234 healthy participants and 3,117 individuals with ASD, we established lifespan brain charts of cortical thickness (CT) and surface area (SA) and derived personalized centile scores indexing deviations from typical neurodevelopment. Using a categorical multilayer community detection framework, we identified three CT-based and three SA-based neuroanatomical subtypes, each characterized by distinct spatial patterns and clinical profiles. Polygenic and plasma proteomic analyses further revealed genetic susceptibility and immune-related pathways underlying the observed heterogeneity. Moreover, the spatial patterns of these subtypes exhibited differential associations with cortical microarchitectural features and aligned closely with multimodal disease epicenters. Collectively, our findings indicate neuroanatomical heterogeneity in ASD as an integrative substrate linking molecular dysregulation to behavioral variability, providing a biologically grounded and clinically relevant framework for parsing the complex mechanisms of autism.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by a constellation of social-affective challenges and restricted, repetitive behaviors that emerge in early childhood and persist across the lifespan¹. Substantial heterogeneity spanning genetic architecture, neurobiology, and clinical presentation poses a major challenge for precision medicine in ASD. This diversity, together with the rising prevalence of the disorder², underscores an urgent need for data-driven frameworks capable of resolving its complex biological underpinnings.

Converging lines of evidence show that autism is marked by profound biological heterogeneity spanning multiple levels of brain organization. Neuroimaging studies reveal diverse patterns of brain abnormalities across individuals with autism^{3,4}, accompanied by widespread alterations in molecular signaling pathways and gene-regulatory processes^{5,6}. Variability in functional connectivity has been linked to differences in the expression of distinct gene sets⁵, suggesting that macroscale circuit dysfunctions may be rooted in spatially patterned molecular architecture. Genetic investigations further indicate that developmental trajectories and polygenic profiles differ according to the age at diagnosis⁷, underscoring the temporally dynamic nature of autism risk. Parallel advances in single-cell genomics have shown that dysregulation within specific gene groups, particularly those expressed in cortico-cortical projection neurons, is associated with variation in clinical symptom severity⁸. Transcriptomic analyses of post-mortem cortex have identified widespread and regionally distributed disruptions in gene expression among autistic donors⁹, reinforcing the view that cortical biology is broadly affected in autism. Complementing these molecular insights, data-driven neuroimaging approaches have begun to uncover patterns of cortical morphological variation that contribute to autism heterogeneity¹⁰. As cortical morphology is both highly heritable and reflective of underlying cytoarchitectural integrity, it serves as a robust intermediate phenotype that bridges genetic variation and neurocognitive diversity¹¹. Together, these findings motivate the hypothesis that atypical cortical morphology represents a critical nexus through which genetic, molecular, and circuit-level mechanisms converge in autism.

Recent work has therefore turned substantial attention to aberrant brain morphometry in autism, revealing pronounced heterogeneity in cortical thickness (CT) and surface area (SA) across multiple cortical systems^{12,13}. Yet, the spatial patterns of morphometric alterations remain inconsistent. For instance, Pretzsch et al.¹⁴ reported that brain structural abnormalities in autism were predominantly driven by sensorimotor regions, whereas Zielinski et al.¹⁵ described atypical changes in frontoparietal and occipital regions, Duan et al.¹⁶ found aberrant alterations in temporal regions, and Khundrakpam et al.¹⁷ identified widespread disruptions across the cortex. This inconsistency may directly stem from the inherent neurobiological heterogeneity of the ASD population, or it could be associated with confounding factors such as limited cohort sizes, narrow age spans, methodological differences, and lack of research focusing on critical early developmental periods such as early childhood^{18,19}. Furthermore, given the nonlinear and regionally specific trajectories of cortical development across the lifespan, a normative modeling framework capable of quantifying individual-level deviations from typical development is essential for resolving this heterogeneity. However, the scarcity of large-scale, lifespan-spanning autism and control cohorts has historically constrained efforts to achieve personalized, lifespan-wide assessments, thereby hindering the identification of stable and reproducible neuroimaging-based biotypes within the ASD population. In parallel, progress toward biologically grounded stratification has been further limited by the lack of large-scale multi-omics datasets in ASD, including genomic and proteomic profiles collected alongside neuroimaging scans. The absence of integrative, cross-modal resources has impeded systematic efforts to link neuroanatomical heterogeneity with its underlying molecular architecture, thereby restricting our ability to define mechanistically informed and clinically actionable subtypes.

To test this hypothesis and overcome previous limitations, we aggregated large-scale lifespan MRI datasets and performed normative modeling in healthy controls (HC) to establish standardized developmental trajectories for CT and SA, enabling the quantification of individual deviations from typical neurodevelopment. Using unsupervised machine-learning approaches, we identified three CT and three SA subtypes, each characterized by distinct spatial patterns of neuroanatomical deviation and dissociable behavioral profiles. To interrogate the biological substrates underlying this heterogeneity, we performed integrative multi-omics profiling, incorporating individual-level genotype data and plasma samples to characterize the polygenic architecture and peripheral molecular signatures associated with each subtype. Multiscale biological annotation further contextualized subtype-specific spatial patterns by mapping them onto cortical microstructural features and putative disease epicenters. Collectively, this integrative framework offers a mechanistic understanding of the autism heterogeneity across hierarchical levels of biological organization.

Results

Participants

After applying a stringent four-step quality control (QC) pipeline²⁰ to evaluate each MRI scan (detailed in Supplementary Methods), the final dataset comprised 60,234 healthy participants (29,802 males; age range, 0–100 years) from 193 sites²⁰, and 3,117 individuals with ASD (2,644 males; age range, 1–62 years) from 36 sites (Fig. 1a and Supplementary Table 1). The ASD MRI cohort included 681 ASD participants from the Autism Brain Imaging Data Exchange (ABIDE I and II)^{21,22} and 2,436 ASD participants from the Shanghai Autism Early Development Cohort (SAED)²³, a large-scale biomedical database that systematically collects neuroimaging data and biospecimens during the early developmental period of autism. Individual-level genotype data was available for 2,566 ASD individuals from the SAED cohort (2,078 males; age range, 1–14 years; mean $\pm$ s.d., 4.72 ± 2.16 years), and 2,312 healthy participants (1,164 males; age range, 4–10 years; 4.83 ± 0.95 years) from the Shanghai Birth Cohort (SBC)²⁴, which is a large-scale population-based cohort designed to investigate the contributions of genetic and environmental factors to child growth and disease risk. Plasma samples were obtained from 251 ASD individuals (212 males; age range, 1–10 years; 4.82 ± 2.08 years) and 90 healthy participants (45 males; age range, 1–10 years; 5.76 ± 2.37 years) in the SAED cohort. Spanning infancy through late adulthood, this integrated ASD dataset offers an unprecedented opportunity to characterize multi-omics profiles underlying neuroanatomical heterogeneity in ASD across the lifespan. An overview of our analytic framework is presented in Fig. 1.

Deviation similarity identified neuroanatomical subtypes in ASD

We implemented standardized MRI image-processing pipelines for all T1-weighted MRI scans^{25,26}, and estimated regional morphometric measures based on the Desikan–Killiany atlas²⁷. Lifespan normative models of the development trajectories of CT and SA were constructed for each brain region using data from 60,234 HC individuals spanning birth to 100 years. Normative models were constructed using the generalized additive model for location, scale and shape (GAMLSS)²⁸, a robust framework for modeling nonlinear growth curves recommended by the World Health Organization²⁹ and most recent neuroimaging studies^{18,20}. This approach captured sex-stratified developmental trajectories across the lifespan while controlling for batch effects. Model parameters were optimized by minimizing the Bayesian information criterion (BIC) to ensure stable and accurate estimation (Supplementary Fig. S1). For each of the 3,117 individuals with ASD, regional centile scores were estimated as age and sex-adjusted offsets relative to the study-specific normative reference trajectories, yielding two deviation matrices (ASD individuals $\times$ brain regions) for CT and SA (Fig. 1b). Centile similarity matrices across individuals were then computed using Pearson's correlation to assess inter-individual similarity in cortical deviation

profiles.

To characterize the pronounced heterogeneity of cortical deviation in ASD, we applied categorical multilayer community detection³⁰ to the concatenated centile-based similarity matrices derived from CT and SA, explicitly accounting for the substantial genetic correlation between these two cortical phenotypes^{11,31}, as well as their within-subject covariance across the brain (Fig. 1c). Rather than analyzing CT and SA separately, concatenating both measures enabled the model to capture shared and complementary sources of neuroanatomical variation, preserving coordinated deviation patterns that may be obscured in a single modality. This joint framework allowed subtype identification to be informed by the integrated morphological architecture of the cortex, rather than by isolated features, thereby improving biological interpretability and robustness. By simultaneously optimizing modularity across multilayer morphological contexts, this approach identified biologically coherent ASD subtypes that more faithfully reflected the multidimensional structure of neuroanatomical heterogeneity.

We identified three CT and three SA subtypes. CT1 was characterized by globally increased cortical thickness except within the salience network, primarily including limbic and insular cortex. In contrast, CT2 exhibited the opposite pattern, with reduced thickness in frontoparietal regions but increased thickness in salience regions. CT3 followed a sensorimotor–association gradient, with thinner sensory and visual cortices while thicker association regions (Fig. 2a). Similarly, SA1 exhibited increased surface area in somatosensory and attention networks while reduced surface area in visual and frontal cortices; SA2 presented the reverse pattern; and SA3 showed globally reduced surface area except in visual regions (Fig. 2b). Interestingly, the spatial deviation patterns observed for the CT and SA subtypes exhibited a graded transition from one polarity to its near inverse. Specifically, the deviation profiles progressed sequentially from CT1 to CT3 to CT2, and from SA1 to SA3 to SA2 (Fig. 2a,b), indicating that neuroanatomical heterogeneity in ASD is organized along a structured continuum, anchored by distinct categorical endpoints. We conducted a series of sensitivity analyses (see Sensitivity Analysis), confirming the robustness of ASD subtype assignment.

Notably, 59.5% of individuals were assigned to different CT and SA communities, suggesting that CT and SA may reflect distinct aspects of ASD heterogeneity (Fig. 2c). We observed significant differences in age distribution across the identified subtypes ($p < 0.001$, one-way ANOVA). Post-hoc analyses revealed that individuals in the CT2 subgroup were significantly younger than those in CT1 and CT3 (Welch's t test, $p < 0.001$; Fig. 2d). Similarly, the SA1 subgroup was significantly older than both SA2 and SA3 (Welch's t test, $p < 0.001$; Fig. 2e). Sex distribution did not differ across CT subtypes (chi-squared test, $p = 0.56$; Fig. 2d), but varied among SA subtypes (chi-squared test, $p = 0.02$; Fig. 2e).

Behavioral performance and clinical symptom severity varied markedly across the defined subtypes

We next assessed group differences across a broad range of behavioral and clinical measures between the identified autism subtypes, including the Childhood Autism Rating Scale (CARS; $n = 2,229$), Autism Diagnostic Observation Schedule (ADOS; $n = 2,253$), Social Responsiveness Scale (SRS; $n = 2,635$), Strengths and Difficulties Questionnaire (SDQ; $n = 2,081$), Social Communication Questionnaire (SCQ; $n = 2,205$), Wechsler Intelligence Scale (IQ; $n = 1,613$), Gesell Developmental Schedules (GDS; $n = 1,192$), Autism Behavior Checklist (ABC; $n = 1,014$), and Vineland Adaptive Behavior Scales (VABS; $n = 855$). These scales comprehensively captured core autism symptoms, social communication deficits, restricted and repetitive behaviors (RRB), emotional and behavioral difficulties, cognitive ability, developmental functioning, and adaptive behavior, enabling a systematic characterization of the clinical phenotypes associated with each neuroanatomical subtype. For comparability across measures, analyses were performed on standardized scale scores⁵ (z-

transformed scale values). Significant differences in clinical symptoms were observed among CT subtypes (p -FDR < 0.05, one-way ANOVA; Fig. 3a, left). In contrast, among SA subtypes, only the SRS-RRB score showed a nominally significant group difference (one-way ANOVA, $F = 6.989$, p -FDR = 0.0451; Fig. 3a, right).

Post-hoc comparisons using Welch's t -tests revealed that individuals in CT2 exhibited more severe symptoms than those in CT1, particularly in domains such as CARS-Listening response (Welch's $t = 5.702$, p -FDR < 0.0001), SDQ-Prosocial behavior (Welch's $t = -5.282$, p -FDR < 0.0001), CARS-Imitative behavior (Welch's $t = 4.576$, p -FDR < 0.0001), CARS-Fear or nervousness (Welch's $t = 3.539$, p -FDR = 0.0012), SCQ-Total (Welch's $t = 3.556$, p -FDR = 0.0012), CARS-Nonverbal communication (Welch's $t = 3.447$, p -FDR = 0.0017), CARS-Total (Welch's $t = 3.476$, p -FDR = 0.0016), and CARS-Verbal communication (Welch's $t = 3.207$, p -FDR = 0.0041) (Fig. 3b). In contrast, individuals in CT3 demonstrated significantly higher verbal IQ (VIQ) compared with CT1 (Welch's $t = 2.221$, p -FDR = 0.0400) and CT2 (Welch's $t = 3.796$, p -FDR = 0.0005), and CT1 showed higher VIQ compared with CT2 (Welch's $t = 2.040$, p -FDR = 0.0416). Similar trends were also observed for full-scale IQ (FIQ) (Fig. 3b).

Polygenic profiles of subtypes

Following stringent genotyping and quality control, we computed polygenic scores (PGSs) for each ASD participant and HC using individual-level genotype data and summary statistics from large-scale genome-wide association studies (GWAS) of ASD-related traits. PGSs analyses revealed a robust autism-related genetic liability in ASD cases compared to HC (Fig. 4a). The strongest association was observed for PGSs derived from earlier-diagnosed ASD (odds ratio (OR) = 1.34, $P < 0.0001$), followed by overall ASD from psychiatric genomics consortium (PGC)³² (OR = 1.21, $P < 0.0001$) and later-diagnosed ASD (OR = 1.10, $P = 0.0006$). Notably, PGSs for age at ASD diagnosis showed an inverse association with ASD status (OR = 0.86, $P < 0.0001$). Cross-disorder effects were also evident, with significant positive associations for schizophrenia (OR = 1.16, $P < 0.0001$), bipolar disorder (OR = 1.09, $P = 0.0032$), attention-deficit/hyperactivity disorder (ADHD; OR = 1.08, $P = 0.0072$), anxiety (OR = 1.06, $P = 0.0411$), and obsessive-compulsive disorder (OCD; OR = 1.06, $P = 0.0426$). Cognitive-related traits, including educational attainment (OR = 1.15, $P < 0.0001$), word reading (OR = 1.08, $P = 0.0109$), spelling (OR = 1.07, $P = 0.0256$), and intelligence (OR = 1.06, $P = 0.0406$), also showed significant associations.

Subtype-specific analyses demonstrated elevated polygenic liability across all ASD subtypes relative to healthy controls, with convergent yet partially distinct genetic profiles across CT and SA dimensions (Fig. 4b). For CT-defined subtypes, all three subtypes showed significant enrichment of ASD-related genetic liability, including PGC overall ASD (CT1: OR = 1.21, $P < 0.0001$; CT2: OR = 1.24, $P < 0.0001$; CT3: OR = 1.21, $P = 0.0010$) and earlier-diagnosed ASD (CT1: OR = 1.31, $P < 0.0001$; CT2: OR = 1.40, $P < 0.0001$; CT3: OR = 1.25, $P = 0.0002$). Later-diagnosed ASD was additionally associated with CT2 (OR = 1.17, $P = 0.0003$) but not CT1 or CT3. PGSs for age at ASD diagnosis showed consistent inverse associations across subtypes (CT1: OR = 0.85, $P = 0.0004$; CT2: OR = 0.85, $P = 0.0004$; CT3: OR = 0.89, $P = 0.0415$). Cross-disorder effects were most prominent in CT2, which exhibited significant associations with schizophrenia (OR = 1.21, $P < 0.0001$), ADHD (OR = 1.12, $P = 0.0117$), bipolar disorder (OR = 1.11, $P = 0.0183$), anxiety (OR = 1.10, $P = 0.0327$), and OCD (OR = 1.16, $P = 0.0011$). In comparison, CT1 was significantly associated with schizophrenia (OR = 1.11, $P = 0.0199$), and CT3 with ADHD (OR = 1.15, $P = 0.0179$). Cognitive traits, including educational attainment (CT1: OR = 1.14, $P = 0.0040$; CT2: OR = 1.13, $P = 0.0052$; CT3: OR = 1.18, $P = 0.0046$), were consistently associated, alongside more selective effects for spelling (CT2: OR = 1.11, $P = 0.0174$; CT3: OR = 1.12, $P = 0.0455$) and word reading (CT2:

OR = 1.13, $P = 0.0054$). Biological age gap (BAG) of brain functional connectivity showed a modest negative association in CT3 (OR = 0.89, $P = 0.0441$).

Similarly, SA-defined subtypes showed associations for ASD-related PGSs, including PGC overall ASD (SA1: OR = 1.21, $P < 0.0001$; SA2: OR = 1.18, $P = 0.0031$; SA3: OR = 1.27, $P < 0.0001$) and earlier-diagnosed ASD (SA1: OR = 1.34, $P < 0.0001$; SA2: OR = 1.30, $P < 0.0001$; SA3: OR = 1.35, $P < 0.0001$). Later-diagnosed ASD was significantly associated with SA2 (OR = 1.13, $P = 0.0232$) and SA3 (OR = 1.18, $P = 0.0005$). Inverse associations with age at diagnosis were again consistent across all subtypes (SA1: OR = 0.88, $P = 0.0034$; SA2: OR = 0.86, $P = 0.0041$; SA3: OR = 0.85, $P = 0.0003$). Cross-disorder associations were most extensive in SA3, including schizophrenia (OR = 1.16, $P = 0.0017$), bipolar disorder (OR = 1.13, $P = 0.0112$), ADHD (OR = 1.12, $P = 0.0156$), anxiety (OR = 1.13, $P = 0.0089$), OCD (OR = 1.10, $P = 0.0424$), and MDD (OR = 1.10, $P = 0.0273$). Cognitive traits were again consistently associated, including educational attainment (SA1: OR = 1.12, $P = 0.0109$; SA2: OR = 1.17, $P = 0.0041$; SA3: OR = 1.15, $P = 0.0021$), intelligence (SA2: OR = 1.15, $P = 0.0105$), spelling (SA2: OR = 1.13, $P = 0.0191$), and word reading (SA1: OR = 1.16, $P = 0.0013$). BAG measures showed significant effects for brain functional connectivity (OR = 0.89, $P = 0.0329$) and immune system (OR = 1.11, $P = 0.0471$) in SA2, and eye in SA1 (OR = 1.09, $P = 0.0447$).

Together, these findings indicate that elevated polygenic liability is shared across neuroanatomical subtypes of ASD, with heterogeneity primarily arising from differential genetic overlap with cognitive traits and other psychiatric disorders.

Subtype-specific plasma proteomics linked to immune

Plasma proteomic profiling revealed both convergent and subtype-specific molecular alterations across ASD subtypes (Fig. 5a,b). A set of proteins was consistently dysregulated, including upregulation of INPP5K and TTR, and downregulation of CASP1 and CDCP1, indicating shared molecular perturbations potentially linked to metabolic dysfunction in ASD.

Functional enrichment analysis of differentially expressed proteins ($p < 0.05$) revealed that immune-related pathways were the most prominently affected across all subtypes, indicating convergent systemic immune involvement. Shared enriched processes included cytokine signaling in the immune system and positive regulation of immune responses (Fig. 5c,d). In parallel, plasma proteins that were exclusively and differentially expressed within specific subtypes delineated distinct pathophysiological mechanisms. Specifically, CT1 was enriched for M-phase cell-cycle regulation and fibrinolysis, CT2 for axon guidance and lymphocyte activation, and CT3 for interferon signaling and complement cascades (Supplementary Fig. S5). SA1 showed unique enrichment for pathways related to *Escherichia coli* infection and apoptosis, SA2 for immunoglobulin-mediated adaptive immunity and phosphate metabolism, and SA3 for platelet activation and adaptive immune response (Supplementary Fig. S5). Notably, adaptive immune response and cytokine signaling in immune system emerged as the most strongly differentiated biological processes across CT and SA subtypes (Fig. 5c,d).

Cognitive and microarchitectural profiling of subtypes

To elucidate the cognitive and neurobiological substrates underlying the subtype-specific deviation patterns, we performed partial least squares (PLS) analysis linking each subtype's centile scores to meta-analytic task activation of 123 cognitive process-related Neurosynth terms^{33,34}, and microarchitectural features³⁵⁻³⁸, including microstructure, metabolism, cortical expansion, cell type-specific gene expression, neurotransmitter receptors and transporters, and mitochondrial profiles.

The statistical significance of the associations was assessed using spatial autocorrelation-preserving permutation tests (spin tests)³⁹, comparing the variance explained by the first latent variable of each PLS model against null models (Fig. 6a). All

associations were significant ($p\text{-spin} < 0.05$), except for the link between SA2 and microarchitecture, and between SA1 and cognitive processes. The PLS models captured substantial covariance between CT and microarchitectural features (CT1: 50.33%, CT2: 50.40%, CT3: 41.33%; Fig. 6a). The latent variable represents the dominant spatial pattern jointly explaining variation in ASD deviation centiles and cognitive processes or microarchitectural features, and the ASD latent scores exhibited high spatial correspondence with the subtype-specific deviation patterns (Fig. 6b).

To identify the features most strongly shaping the shared spatial patterns, we correlated each measure with the PLS-derived score maps to derive loading coefficients, quantifying each feature's contribution to the latent variables. Firstly, we found that cognitive processes contributed differentially to the subtypes (Fig. 6c). CT1 predominantly reflected perceptual–motor processes, exhibiting large positive loadings on gaze, imagery, and action, alongside negative loadings on emotion, valence, and stress. In contrast, CT2 captured heightened affective–salience engagement, showing large positive loadings on fear, anxiety, and stress, and negative loadings on planning, skill, and action. CT3 was biased toward emotional processes, with large positive loadings on emotion, arousal, and valence, and negatively correlated to multisensory integration, imagery, and fixation. SA1 highlighted a sensorimotor–affective dissociation, with large positive loadings on imagery, movement, and coordination, and negative loadings on valence, emotion, and mood. By contrast, SA2 exhibited a nearly inverse profile, emphasizing emotional and affective processes at the expense of sensorimotor functions. SA3 was characterized by a visual–perceptual profile, with large positive loadings on fixation, object recognition, and visual attention, and negative loadings on response inhibition, cognitive control, and inhibitory processes.

Secondly, parallel analyses revealed distinct microarchitectural substrates across subtypes (Fig. 6d). CT1 was characterized by strong positive loadings on microstructural features, including the first principal component of gene expression derived from Allen Human Brain Atlas (AHBA gene PC1), myelination, and the E/I ratio, as well as metabolic measures such as oxygen metabolism, cerebral blood flow, glucose metabolism, and cerebral blood volume, alongside neuron-specific gene expression. These were opposed by large negative loadings on glial-specific gene expression (oligodendrocyte progenitor cells, astrocytes, microglia) and neurotransmitter receptors and transporters (MOR, 5HT1a, D2, CB1, D1, DAT, 5HTT). By contrast, CT2 exhibited the inverse profile, with strong positive associations with monoaminergic receptors (5HTT, 5HT1a, DAT, D2, D1, 5HT4) and glial-specific gene expression, and negative associations with metabolic indices (glycolytic index, glucose metabolism, cerebral blood flow, oxygen metabolism), neuron-specific gene expression, synapse density, and additional receptors (A4B2, 5HT1b, NET). CT3 was defined by positive loadings on receptors (MOR, CB1, D2, 5HT1a, H3, 5HT4), glial gene expression, and cortical expansion, opposed by negative loadings on microstructural and metabolic features. Similarly, SA1 and SA2 were predominantly shaped by glial and neurotransmitter-related features, showing strong positive loadings on glial-specific gene expression and receptors (5HT1a, D2, 5HT4, MOR, CB1, 5HTT), and negative loadings on microstructural and metabolic measures. In contrast, SA3 was anchored by positive loadings on metabolic and microstructural indices, accompanied by negative associations with receptors (MOR, CB1, H3, mGluR5, A4B2, D2), glycolytic index, and cortical expansion.

Multimodal disease epicenters of subtypes

Autism-related cortical perturbations are unlikely to originate from isolated loci; instead, they are expected to propagate through coordinated molecular, anatomical, and functional networks to influence distributed brain systems. To test this hypothesis and delineate the network architecture underlying subtype-specific deviation patterns, we performed epicenter mapping by correlating each region's normative connectivity profile, derived from gene expression similarity, receptor

density similarity, glucose metabolic connectivity, electrophysiological coupling, functional connectivity, and structural connectivity, with the cortical deviation maps of each subtype.

Distinct spatial distributions of multimodal epicenters were observed across subtypes (Fig. 7a,b). CT1 exhibited epicenters predominantly within occipital regions, suggesting a pathology primarily affecting the visual cortex. CT2 was characterized by epicenters in the temporal and limbic cortices, implicating disruptions associated with socio-emotional processing and interoceptive integration. In contrast, the frontoparietal localization of CT3 epicenters suggested dysfunction targeting the brain's integrative hub for executive control and complex cognition (Fig. 7a). The SA subtypes displayed greater spatial heterogeneity across modalities. SA1 demonstrated distributed epicenters spanning sensorimotor, frontoparietal, temporal, and limbic regions, indicating multimodal anchoring spanning perceptual and affective systems. SA2 revealed epicenters concentrated in the frontal and limbic system, indicative of disrupted top-down cognitive control. SA3 showed preferential epicenter localization within occipital cortices, suggesting alterations in visual perception (Fig. 7b).

We next quantified the associations between each subtype's deviation pattern and its corresponding multimodal epicenter maps. The epicenter profiles were significantly strongly correlated with the deviation patterns across modalities (p -spin < 0.05, Fig. 7c), with structural connectivity most often showing the strongest correspondence, followed by gene expression similarity (Fig. 7d). This hierarchy suggests that the propagation of cortical perturbations in autism may preferentially follow white-matter and molecular pathways.

Sensitivity analyses

To evaluate the robustness and reproducibility of both normative neurodevelopmental trajectories and the autism subtypes, we conducted a series of sensitivity analyses at the stages of model fitting and subtype identification.

First, to assess the stability of the lifespan normative trajectories, we conducted 1,000 bootstrap resampling iterations for each measure and refitted the GAMLSS models. The estimated developmental trajectories showed highly consistent age-related trends across bootstrap iterations, with minimal variation in curve shape and percentile distribution (Supplementary Fig. S2–4). Confidence intervals remained narrow across the lifespan, indicating that the fitted normative trajectories were not driven by specific samples, outliers, or site-specific effects, but instead captured stable population-level developmental patterns.

Second, to examine the reproducibility of the autism subtypes derived from individualized deviation profiles, we performed subsampling validation of the categorical multilayer community detection. In each iteration, we randomly selected 50–80% of individuals with ASD using stratified sampling by sex, age (quantile-binned to preserve balanced representation across developmental stages), and study, thereby minimizing potential confounding introduced by demographic imbalance or site heterogeneity. For each subsampled dataset, we repeated the entire multilayer community detection, including modularity optimization and consensus partitioning, using the same parameter settings as in the primary analysis, and performed 1,000 optimization runs per subsampling proportion to ensure partition stability. This approach allowed us to determine whether the identified subtype structure was disproportionately influenced by specific individuals or sample composition. Across all subsampling proportions, the global deviation patterns, community assignments, and cortical signatures remained highly concordant with the primary findings, demonstrating strong reproducibility of the ASD subtypes (Supplementary Fig. S6).

Collectively, these sensitivity analyses provide convergent evidence that both the normative neurodevelopmental models and the downstream subtype classification are robust to sampling variability and methodological perturbation, supporting

the reliability of the identified autism subtypes.

Discussion

In this study, we aggregated large-scale MRI data from 60,234 HCs to construct normative lifespan growth charts. These normative models provided personalized quantification of neuroanatomical deviation from typical neurodevelopment for 3,117 participants with ASD. Using unsupervised machine learning, we identified three CT and three SA subtypes defined by distinct spatial patterns of cortical perturbation. Leveraging multi-omics data, we revealed that these subtypes exhibited differentiated associations with clinical symptomatology, polygenic liability, and plasma proteomic signatures. Moreover, the neuroanatomical deviation patterns of each subtype demonstrated divergent alignment with microarchitectural features and disease epicenters. Collectively, these findings position neuroanatomical heterogeneity as a critical organizing axis of autism, linking distributed genetic and molecular influences to emergent behavioral variability across the spectrum.

CT subtypes were characterized by significantly divergent deviation patterns across brain systems. CT1 was characterized by widespread expansion except for the salience-related regions, particularly the insular and limbic networks. CT2 showed the nearly opposing pattern. The salience network is engaged in multiple brain functions associated with sensory integration and attention^{40,41}, responsible for monitoring the interoceptive and exteroceptive sensory stream, detecting subjectively salient stimuli, and guiding attention accordingly⁴². Our results are consistent with previous findings that dysregulation of salience-processing systems can be a distinguishing feature and predictor for symptom severity in children with ASD⁴³, and insular dysfunction may be a common transdiagnostic characteristic⁴⁴. The opposite deviations between salience and other networks observed here may therefore signify a desynchronization between interoceptive–affective and cognitive–perceptual systems, leading to instability in network coordination and inefficient information integration hypothesized to underlie the social and cognitive difficulties in autism. In addition, CT3 was distinguished by expansion in frontoparietal and temporal regions but atrophy in sensory and visual cortices. This profile aligns with the notion of developmental imbalance between higher-order cognitive control and perceptual processing systems^{18,45}, possibly reflecting compensatory reorganization in individuals with autism.

In contrast, SA subtypes exhibited completely different deviation patterns compared to the CT subtypes. SA1 and SA2 exhibited nearly opposing patterns, particularly across visual, somatosensory, and frontoparietal networks, whereas SA3 presented a predominantly global reduction except for the visual cortex. Given that surface area primarily reflects early progenitor proliferation and tangential expansion⁴⁶, these contrasting patterns likely index divergent alterations in cortical arealization⁴⁷. The reciprocal deviations between different cortical networks further suggest imbalanced scaling along the cortical hierarchy, potentially reflecting heterogeneity in maturational timing and neurogenetic gradients^{48,49}. Such system-specific divergence may contribute to the impaired sensory processing and top-down regulation of behavior observed in autism^{50,51}, thereby highlighting multiple developmental routes to cortical atypicality.

Interestingly, the spatial deviation patterns of CT and SA subtypes exhibited a graded transition across subtype boundaries rather than sharply discrete separations. Specifically, the deviation profiles progressed sequentially from CT1 through CT3 to CT2, and from SA1 through SA3 to SA2, suggesting that the neuroanatomical heterogeneity of ASD is characterized as a structured continuum with distinct categorical anchors rather than as entirely independent and isolated subgroups¹⁰. This pattern indicates that ASD-related cortical alterations may be organized along latent neurodevelopmental axes^{52,53}, where individuals occupy different positions within a spectrum of atypical brain maturation, while still clustering around stable subtypes. This finding also helps reconcile the long-standing tension between categorical and dimensional models of autism.

Traditional approaches often assume a single average ASD phenotype, whereas dimensional models emphasize continuous variation across individuals⁵⁴. Our results support an intermediate perspective: ASD heterogeneity may be fundamentally dimensional, but this variation organizes into clusters that are clinically and biologically meaningful. Rather than being contradictory, these observations may reflect different resolutions of the same underlying developmental landscape.

In this context, CT2 exhibited a younger age yet more severe clinical symptoms, together with an opposite deviation pattern within the insular and limbic systems compared to CT1, suggesting the presence of a possible pathological axis anchored in the salience system, driving a cascading neurodevelopmental desynchronization underlying the variation in symptom severity across subtypes. The salience network undergoes temporally and spatially coordinated maturation during early life, paralleling progressive refinement in socioemotional, attention, and cognitive processing⁴². Aberrations in these processes, potentially reflecting dysregulated synaptic pruning⁵⁵ or atypical maturational trajectories¹⁴, may disrupt the hierarchical tuning of large-scale neural circuits in autism. In particular, insular dysfunction could impair the encoding of social interaction, social decision-making, emotion, and empathy⁵⁶. Such desynchronization within the salience system may mechanistically explain the pervasive difficulties in social communication and behavioral flexibility frequently observed in autistic individuals^{57,58}. CT3 exhibited a higher IQ compared to other CT subtypes, accompanied by a deviation pattern along the sensorimotor–association axis. The frontoparietal network, recruited by a broad range of different cognitive demands, has been linked to intelligence in multiple studies^{59,60}. Increased cortical thickness in these regions may reflect delayed cortical pruning or prolonged synaptic maintenance, processes that can transiently enhance cognitive capacity by preserving neural plasticity. This interpretation aligns with the prior evidence that slower cortical thinning in frontoparietal regions correlates with superior cognitive performance⁶¹. Such expansion may thus represent a compensatory recruitment of higher-order networks that sustains cognitive ability in the presence of neurodevelopmental perturbations.

Polygenic risk profiling revealed that genetic liability for ASD is not monolithic but distributed along a graded continuum across related traits. The most pronounced association was observed for earlier-diagnosed ASD, followed by attenuated effects for later-diagnosed ASD, and an inverse relationship with age at diagnosis. This gradient suggests that the timing of symptom emergence is, at least in part, genetically modulated rather than solely shaped by environmental exposures⁷, consistent with a developmental liability model in which higher inherited burden accelerates phenotypic manifestation⁶².

Beyond ASD-specific risk, elevated polygenic loading for co-occurring psychiatric conditions and cognitive traits supports a shared genetic architecture across neurodevelopmental and psychiatric domains⁶³. Notably, although all neuroanatomical subtypes demonstrated increased ASD-related polygenic risk and elevated polygenic liability for educational attainment, CT2 and SA3 exhibited broader pleiotropic profiles in psychiatric disorders, spanning ADHD, schizophrenia, OCD, bipolar disorder, and anxiety, alongside cognitive traits and biological age gaps of organs. By contrast, the remaining subtypes displayed comparatively restricted and heterogeneous patterns of association with psychiatric polygenic risk. This pattern indicates that subtype-defining cortical deviations are not epiphenomenal but reflect biologically meaningful stratification of inherited liability. Thus, rather than a single etiological pathway, ASD appears to arise from partially overlapping yet divergent configurations of polygenic liability⁶⁴. This divergence highlights a stratified genetic landscape, in which only a subset of neuroanatomical configurations captures a generalized liability that bridges neurodevelopmental, psychiatric, cognitive, and organismal ageing processes, whereas others may reflect more circumscribed or distinct etiological pathways.

Plasma proteomic profiling revealed both convergent and subtype-specific molecular alterations. Consistent dysregulation of immune-related plasma proteins suggests that immune processes may act as central mediators linking brain phenotypes

and peripheral physiological changes in autism⁶⁵. Such immune perturbations could drive elevations in cytokine levels, contributing to neuroinflammation and consequent cognitive and behavioral impairments⁶⁶. Synaptic-immune signaling engages a range of molecular pathways that can be disrupted by genetic variants or environmental exposures associated with autism, thereby altering neural development and circuit function⁶⁵. Beyond these convergent pathways, distinct proteomic fingerprints within subtypes further suggested that heterogeneity extends from neural architecture to peripheral immune systems⁶⁷. The association between cortical and plasma-level differentiation highlights coordinated neuroimmune and metabolic coupling across biological scales, whereby distinct developmental deviation and immune dysregulation may jointly shape the phenotypic diversity of autism.

The dissociation between subtypes linked to microstructural and metabolic features and those preferentially associated with neuroglia and monoaminergic systems suggests that autism heterogeneity may arise from distinct biological constraints on neurodevelopment, rather than from a single pathology. This divergence is consistent with the pronounced developmental asynchrony and cognitive variability that may bias individuals with autism toward different clinical presentations⁶⁸⁻⁷⁰. Subtypes coupled to cortical microstructure and metabolism likely index intrinsic constraints on intracortical myelination and regional energetic capacity that collectively determine the hierarchical coordination of cortical maturation^{71,72}. These processes govern conduction velocity and the stabilization of neural circuits, thereby setting the fundamental biophysical scaffold upon which higher-order function is built^{73,74}. Disruption along this axis may therefore preferentially affect circuits with early and energetically demanding maturation trajectories, and increase the cost of long-range integration. By contrast, subtypes associated with glia and monoaminergic signaling implicate a complementary developmental regime dominated by synaptic regulation and neuromodulatory control^{36,75}. Astrocytes and microglia coordinate synapse formation, pruning, and myelin remodeling⁷⁵⁻⁷⁷, while dopamine and serotonin provide modulatory signals that dynamically tune excitability, plasticity, salience, and affective state across distributed cortical networks⁷⁸. Perturbations within this axis may therefore exert broad effects on social salience and cognitive flexibility.

Epicenter analyses further revealed that subtype-specific cortical perturbations were embedded within, and potentially propagated through, the brain's molecular and structural architecture. Distinct epicenter patterns across subtypes highlight that cortical deviations do not emerge in isolation but follow the intrinsic organization of large-scale networks. Subtypes anchored in sensory and perceptual territories suggest early developmental vulnerability within bottom-up processing streams^{79,80}, whereas those centered on temporal-insular and frontoparietal regions implicate higher-order association systems mediating socio-emotional and executive functions⁸¹. The preferential alignment of deviation patterns with structural and gene expression similarity indicated that white-matter pathways and molecular gradients may scaffold the spatial spread of cortical atypicality^{82,83}. This hierarchical propagation suggested that local neurodevelopmental disruptions could cascade along connected circuits, giving rise to the distributed yet system-specific cortical alterations characteristic of autism⁸⁴.

Our study has several limitations. First, the normative models were constructed using aggregated MRI datasets from diverse cohorts across continents, scanners, and demographic backgrounds. Although we incorporated batch effects as random factors to mitigate potential confounds, a strategy widely endorsed in previous large-scale neuroimaging studies^{18,20}, future consortia-based efforts employing standardized acquisition protocols and balanced demographic representation will be critical for refining lifespan trajectories. Second, the age distribution of individuals with ASD was skewed toward childhood. Our derived neuroanatomical subtypes may not fully capture the phenotypic heterogeneity that emerges by adulthood. Third, the GWAS summary statistics used for polygenic score construction was derived from European-ancestry cohorts

due to the lack of large-scale ASD-related GWAS in East Asian populations. This ancestral mismatch between the GWAS and our genotyped sample may reduce predictive accuracy and attenuate effect sizes due to differences in allele frequencies, linkage disequilibrium structure, and genetic architecture across populations. Fourth, the microstructural profiles, cognitive processes, and cortical connectomes were derived from publicly available datasets of neurotypical individuals, which may not fully capture autism-specific molecular or circuit-level alterations. Fifth, the plasma proteomic subsample was modest relative to the MRI cohort, potentially reducing sensitivity to subtle molecular effects. Finally, while PLS analysis enabled the identification of cross-domain associations, it remains a linear approach that cannot fully capture the nonlinear and hierarchical mechanisms underlying autism pathology.

In summary, we delineated a systematic framework for parsing the neuroanatomical heterogeneity of autism by integrating large-scale neuroimaging datasets with multi-omics profiling. Our findings help reconcile a central paradox in autism: how a clinically heterogeneous condition can arise from diverse yet systematically patterned neurobiological substrates. We found that the neuroanatomical heterogeneity in autism is not a monolithic entity but organized along distinct genetic and molecular axes that dissociate across cortical systems. Notably, the convergence of cortical and proteomic alterations highlights a key role of immune dysregulation. Collectively, these findings suggested that neuroanatomical heterogeneity constitutes a core organizing principle of autism, bridging molecular perturbations with large-scale brain architecture and phenotypic diversity.

Methods

Ethics

The present study was approved by the Ethics Committee of Xinhua Hospital affiliated with Shanghai Jiao Tong University School of Medicine (XHEC-C-2019076) and was registered at ClinicalTrials.gov (NCT04358744). All contributing datasets were conducted in accordance with protocols approved by the Institutional Review Boards of the original studies, and informed consent was obtained from all participants or their legal guardians.

Participants

In this study, we used large-scale multisite neuroimaging datasets following rigorous quality control procedures. The final sample comprised 60,234 HC participants (29,802 males; aged 0–100 years) from 193 sites²⁰ and 3,117 individuals with ASD (2,644 males; aged 1–62 years) from 36 sites. To capture neuroanatomical heterogeneity within the autism population across the lifespan, we integrated two complementary ASD cohorts: the widely utilized ABIDE I and II neuroimaging datasets ($n = 681$; aged 5.1–62 years), and the SAED cohort ($n = 2,436$; aged 1–14.5 years), a large-scale multi-omics initiative focused on the early childhood development in ASD. For the SAED cohort, clinical diagnoses were made by experienced clinicians based on the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5)⁸⁵ and were confirmed using the age-appropriate modules of the Autism Diagnostic Observation Schedule (ADOS)⁸⁶. Specifically, the standard ADOS module 1 for children over 30 months of age and the ADOS Toddler Module for those between 12 and 30 months. None of the ASD children diagnosed before 30 months of age had any change in diagnosis during subsequent follow-up visits. The ADOS calibrated severity scores were calculated to allow the comparison of autism severity across participants tested with different ADOS modules⁸⁷. The neurocognitive assessment was made around their first MRI visit. The DQ was assessed by the Gesell Developmental Schedules (GDS)⁸⁸ for children younger than 4 years. The IQ was assessed by the Wechsler Preschool and Primary Scale of Intelligence (WPPSI)⁸⁹ for 4- to 6-year-old children and the Wechsler Intelligence Scale for Children-Revised (WISC-R)⁹⁰ for children older than 6 years. The Childhood Autism Rating Scale (CARS)⁹¹ and Social Responsiveness Scale (SRS)⁹² were used to assess social-related clinical phenotypes. All participants had no neurological issues, such as suspected vision problems, hearing problems, known genetic disorders, or neurological conditions. Informed consent was obtained from the parents or guardians of each participant.

Individual-level genotype data were available for 2,566 individuals with ASD from the SAED cohort (2,078 males; aged 1–14 years) and 2,312 HC individuals from the SBC cohort (1,164 males; aged 4–10 years). Plasma samples for proteomic profiling were obtained from 251 individuals with ASD (212 males; aged 1–10 years) and 90 HC participants (45 males; aged 1–10 years) within the SAED cohort. Detailed demographic characteristics are provided in Supplementary Table 1.

MRI quality control and processing

To ensure the high quality of neuroimaging data and enhance the credibility of our findings, we implemented a rigorous and standardized QC pipeline for all MRI scans using a comprehensive four-step QC framework²⁰ that integrated automated quality assessment tools, including MRIQC and FSQC⁹³, as well as custom scripts, followed by expert visual inspection of each MRI scan (detailed in Supplementary Methods). This systematic approach was designed to detect and exclude scans with excessive head motion, low signal-to-noise ratio, structural artifacts, poor tissue segmentation, or inaccurate surface reconstruction, thereby improving the reliability and robustness of downstream analyses. Given the pronounced anatomical changes in the cerebral cortex across the human lifespan, particularly during the perinatal and early infancy periods, there

is currently no unified processing protocol universally applicable across all ages. To maximize the accuracy and robustness of MRI data processing, we employed age-specific strategies consistent with our prior work²⁰ (detailed in Supplementary Methods). Brain morphometric measures, including cortical thickness and surface area, were estimated based on the Desikan-Killiany atlas²⁷ and the reconstructed cortical surfaces.

Normative modeling and centile scores

To accurately estimate sex-stratified normative brain development trajectories corrected for batch effects, we employed the GAMLSS²⁸ framework using 60,234 HC individuals aged 0 to 100 years. GAMLSS offers a flexible and robust statistical framework capable of modeling both linear and nonlinear age-related changes, as well as the estimation of study-specific offsets. This method is endorsed by the World Health Organization²⁹ and has been widely adopted for estimating growth trajectories in neurodevelopmental studies^{18,20}. The growth curve of regional morphometric measures (CT/SA) was modeled using GAMLSS with a generalized gamma distribution $GG(\mu, \sigma, \nu)$ ¹⁸. Model parameters were linked to an additive equation comprising fixed effects (sex), random effects (site-processing pipeline), and fractional polynomial transformation terms of age¹⁸. To ensure optimal model performance, we systematically explored multiple configurations for fractional polynomial parameterizations, selecting the model with the lowest BIC as the best-fitting specification (Supplementary Fig. S1). The reliability and robustness of the resulting normative models were further validated using 1,000 bootstrap resampling iterations (Supplementary Fig. S2-4).

The estimated normative trajectories of brain development enabled quantification of each individual with ASD relative to age-normed, sex-stratified distributions. For all 3,117 participants with ASD, centile scores were calculated with reference to the normative growth curves¹⁸, yielding standardized metrics of morphometric divergence from typical development.

Categorical multilayer community detection

To assess inter-individual similarity in morphometric deviations among individuals with autism, we calculated Pearson's correlation coefficients between participants' regional centile scores, separately for CT and SA, yielding two subject-by-subject similarity matrices. After excluding negative correlations, we applied Fisher's z-transformation to the remaining correlation coefficients to enhance the normality of distributions.

We then applied categorical multilayer community detection³⁰, a robust and effective approach for capturing complex multilayer modular structures, to the concatenated similarity matrices. This method optimizes the multi-slice modularity quality function, which leverages the relative densities of intra- and inter-community connections to partition subjects into communities, where individuals within the same community exhibit similar deviation patterns, whereas those in different communities show weaker resemblance. The multilayer modularity function is defined as:

$$Q_{\text{multilayer}} = \frac{1}{2\mu} \sum_{ijsr} [(A_{ijs} - \gamma_s V_{ijs})\delta_{sr} + \delta_{ij}\omega_{jsr}]\delta(g_{is}, g_{jr})$$

where layer s/r corresponds to one of the two brain measurements, A_{ijs} represents the deviation similarity matrix of slice s , and V_{ijs} denotes the corresponding intralayer Newman-Girvan null model. The parameter γ_s controls the topological resolution of slice s and ω_{jsr} is the coupling parameter linking subject j between layer r and s . The Kronecker delta function $\delta(g_{is}, g_{jr})$ is 1 if subject i in slice s and subject j in slice r belong to the same community and 0 otherwise. The parameters $\gamma = 1$ and $\omega = 1$ were selected to achieve a balanced trade-off between intra-layer structure and inter-layer

consistency. This parameter combination yielded stable community assignments while retaining sufficient sensitivity to capture meaningful dynamic reconfigurations across brain measures, thereby minimizing both over-fragmentation and excessive smoothing of community modules. To ensure the robustness of the community consensus, we performed 1,000 optimizations of the model fitting process, ultimately obtaining community assignments for each cortical feature.

Statistical analysis

To characterize the spatial deviation pattern within the identified ASD subtypes (communities), we performed one-sample *t*-tests on regional centile scores for each subtype and measure, with multiple comparisons controlled using the Benjamini-Hochberg false discovery rate (FDR, $p\text{-FDR} < 0.05$). To assess the robustness of community assignment and the stability of deviation patterns, we repeated the categorical multilayer community detection analyses on randomly subsampled ASD cohorts, varying the sampling proportion from 50% to 80% (see Sensitivity Analysis; Supplementary Fig. S6). Behavioral performance and clinical symptom differences across subtypes were evaluated using one-way ANOVA and Welch's *t*-tests across a broad set of measures. Statistical significance was corrected using FDR, with a threshold set at $p\text{-FDR} < 0.05$.

Genotype quality control and processing

Genotypes were processed for SAED autism cases and SBC controls aligned to GRCh38/hg38. Initial QC removed variants with >5% genotype missingness and samples with >2% missingness, retaining only biallelic autosomal SNPs with A/C/G/T alleles and removing monomorphic sites (minor allele count, MAC < 1). Stringent variant-level QC was applied, including Hardy-Weinberg equilibrium (exact mid-*p* test; $p < 1 \times 10^{-6}$) in confirmed controls only, differential missingness testing between confirmed cases and controls (mid-*p*, $p < 1 \times 10^{-5}$), and removal of duplicate variant IDs. To minimize linkage disequilibrium (LD) inflation, heterozygosity metrics were estimated on an LD-pruned autosomal marker set excluding long-range LD regions (indep-pairwise 50 5 0.2). Samples with extreme inbreeding coefficients ($|F| > 0.2$) were excluded, and individuals exceeding ± 5 s.d. in heterozygosity were flagged for review. Pairwise relatedness was inferred from an LD-pruned set of autosomal variants (chr1–22; minor allele frequency, MAF ≥ 0.05 ; SNP missingness $\leq 2\%$; indep-pairwise 100 50 0.1; excluding long-range LD regions), and identity-by-descent statistics were computed using PLINK^{94,95}. Individuals related at second-degree or closer (PI_HAT > 0.1875) were pruned by removing one sample per pair according to a deterministic prioritization rule: higher sample missingness first; if tied, the sample participating in more related pairs was removed; remaining ties were resolved by removing the second sample in the pair. The final pre-imputation dataset was defined by applying a MAF threshold (MAF ≥ 0.01), and population structure was summarized using principal components analysis with a LD-pruned marker set (MAF ≥ 0.05 , SNP missingness $\leq 2\%$, HWE $p \geq 1 \times 10^{-6}$, indep-pairwise 50 5 0.2; excluding long-range LD regions), and the cleaned dataset was split by chromosome for imputation.

Post-imputation genotype data were obtained from the ChinaMAP⁹⁶ server as per-chromosome dosage VCFs and indexed with tabix, yielding 58,504,309 autosomal variants prior to imputation-quality filtering. Variants with imputation quality (R^2) ≥ 0.6 were retained and concatenated into a cohort-level VCF comprising 20,681,789 variants. The merged data were converted to PLINK format, restricting to biallelic A/C/G/T SNPs and standardizing variant identifiers, with no duplicate variants detected. Sample identifiers were harmonized, and phenotype and sex annotations were assigned from curated metadata. Post-imputation quality control applied filters for genotype missingness ($\leq 5\%$) and minor allele frequency (MAF ≥ 0.01), removing 14,282,630 low-frequency variants and retaining 6,399,159 variants. No variants failed Hardy-Weinberg equilibrium testing in controls (exact mid-*p* test; $p < 1 \times 10^{-6}$), and no samples were excluded due to missingness. The final dataset comprised 6,399,159 high-quality variants for downstream analyses.

Polygenic scores

Polygenic scores (PGSs) were derived from the most recent well-powered GWAS of ASD, ASD-related traits, co-occurring psychiatric disorders, and multi-organ biological age gap (BAG). Specifically, summary statistics were obtained for ASD^{7,32} (including ASD, earlier-diagnosed ASD, later-diagnosed ASD, and age at ASD diagnosis), attention-deficit/hyperactivity disorder⁹⁷ (ADHD), major depressive disorder⁹⁸ (MDD), schizophrenia⁹⁹, obsessive-compulsive disorder¹⁰⁰ (OCD), bipolar disorder¹⁰¹, anxiety¹⁰², anorexia nervosa¹⁰³, intelligence¹⁰⁴, educational attainment¹⁰⁵, spelling, and word reading¹⁰⁶. PGSs were also generated for BAG phenotypes^{107,108} encompassing grey matter, white matter, functional connectivity, brain, eye, pulmonary, cardiovascular, liver, kidney, metabolic, immune, and musculoskeletal domains. All variants in the GWAS summary statistics were converted from GRCh37/hg19 to GRCh38/hg38 via liftOver¹⁰⁹ to align with the genotype data. PGSs were computed for individuals with available genotyping array data using PRS-CSx^{110,111} (v.1.1.0), a Bayesian polygenic prediction framework that infers posterior single-nucleotide polymorphisms (SNPs) effect sizes by integrating GWAS summary statistics with an external linkage disequilibrium reference panel under a continuous shrinkage prior. Associations between each trait-specific PGS and ASD subtypes were evaluated using logistic regression models. Odds ratios (ORs) and corresponding 95% confidence intervals were estimated, adjusting for age, sex, and the first ten genetic principal components.

Plasma proteomics

Blood samples were centrifuged at room temperature for 10 min, aliquoted, and frozen at -80°C within 30 min of collection. For processing, samples were transferred to 1.5 mL Eppendorf tubes and adjusted to 100 μL with 50 mM ammonium bicarbonate. Proteins were denatured by heating at 95°C for 3 min, cooled to room temperature, and digested with trypsin at 37°C for 16 h. Resulting peptides were extracted, lyophilized, and desalted. Lyophilized peptides were reconstituted in 100 μL of 0.1% formic acid, and 2% of the solution was injected for mass spectrometry analysis.

In the mass spectrometry data acquisition, samples were separated using an EASY-nLC 1200 nano-flow high-performance liquid chromatography (HPLC) system. Mobile phase A consisted of 0.1% formic acid in water, while mobile phase B comprised 0.1% formic acid in acetonitrile (80% acetonitrile). Prior to sample loading, the trap and analytical columns were equilibrated with 100% mobile phase A. The digested peptide samples were then delivered to the trap column (2 cm, ID 100 μm , 3 μm , C18) via an autosampler and subsequently separated using an analytical column (15 cm, ID 150 μm , 1.9 μm , C18) at a flow rate of 600 nL/min.

Following chromatographic separation, mass spectrometry analysis was performed using an HFX mass spectrometer in positive ion mode. The precursor ion scan range was set to 300–1400 m/z , with a first-stage mass resolution of 60,000 at 200 m/z . The automatic gain control (AGC) target was set to $3e6$, with a maximum injection time of 20 ms. Peptide and peptide fragment mass-to-charge ratios were acquired using the following method: after each full scan, 30 data-independent acquisition (DIA) scans were collected using higher-energy collisional dissociation (HCD) with a normalized collision energy of 27%. The isolation window varied according to the isolation scheme, and the second-stage mass resolution was set to 15,000 at 200 m/z . The raw mass spectrometry data were then processed using the iProteome cloud-based platform for qualitative protein analysis.

Enrichment analyses

Group differences in plasma proteomic profiles were assessed using one-way ANOVA and Welch's t -tests. Functional

enrichment analyses were subsequently performed using Metascape¹¹², an automated platform for integrative meta-analysis, to identify biological processes and pathways associated with candidate protein-encoding genes. Analyses were conducted for proteins significantly up- or down-regulated ($p < 0.05$) in ASD subtypes compared to HC, as well as between subtypes. Enrichment p -values were calculated using the cumulative hypergeometric test and corrected using FDR.

Cognitive and microarchitectural brain maps

We utilized meta-analytic activation maps from Neurosynth (<https://neurosynth.org>), a platform that provides probabilistic associations between brain regions and cognitive processes derived from more than 14,000 functional MRI studies. While the full Neurosynth database includes over 1,300 terms, we refined our analysis to 123 terms relevant to cognition, behavior, and emotion, selected from the Cognitive Atlas, an open-access ontology of cognitive neuroscience^{33,34}. The probabilistic measures estimated by NeuroSynth provide a quantitative representation of the strength of association between regional brain activity and cognitive processes.

We further aggregated multi-level cortical profiles from the neuromaps toolbox (<https://github.com/netneurolab/neuromaps>) and the NeuroVault repository (<https://neurovault.org>). These brain maps encompassed measures of cortical microstructure, metabolism, neurotransmitter receptor distribution, mitochondrial function, cortical expansion, and cell-type-specific gene expression. Surface-based data were transformed into the fsLR32k space via linear interpolation and parcellated using the Desikan-Killiany atlas in fsLR32k space. Volumetric profiles were retained in their native MNI152 volumetric space and were parcellated into the Desikan-Killiany atlas in MNI152 space.

Microstructural brain maps included the T1w/T2w ratio¹¹³ (as a proxy for myelination), the first principal component of gene expression from the Allen Human Brain Atlas (AHBA)¹¹⁴, the excitatory-to-inhibitory receptor density ratio¹¹⁵, and synaptic density estimated via [¹¹C]UCB-J PET tracer binding to synaptic vesicle glycoprotein 2A (SV2A)¹¹⁶. Metabolic brain maps encompassed the glycolytic index, cerebral blood flow and volume, as well as glucose and oxygen metabolism¹¹⁷. Cortical expansion maps included evolutionary and developmental expansion¹¹⁸, and allometric scaling¹¹⁹. Neurotransmitter maps comprised density distributions for 18 receptors and transporters, including serotonin (5-HT1a, 5-HT1b, 5-HT2a, 5-HT4, 5-HT6, 5-HTT), dopamine (D1, D2, DAT), norepinephrine (NET), histamine (H3), acetylcholine ($\alpha 4\beta 2$, M1, VACHT), cannabinoid (CB1), opioid (MOR), glutamate (mGluR5), and GABA (GABAA/bz)³⁶. Cell-type-specific gene expression profiles were derived based on the AHBA dataset¹²⁰, including astrocytes (astro), oligodendrocytes (oligo), oligodendrocyte precursor cells (opc), endothelial cells (endo), microglia (micro), excitatory neurons (neuron-ex), and inhibitory neurons (neuron-in). Mitochondrial features³⁷ included tissue respiratory capacity (TRC), mitochondrial respiratory capacity (MRC), and mitochondrial density (MitoD), along with three markers of oxidative phosphorylation (OXPHOS) enzyme activity reflecting cellular energy-transformation capacity: complex I (CI; NADH-ubiquinone oxidoreductase), complex II (CII; succinate dehydrogenase), and complex IV (CIV; cytochrome *c* oxidase).

Partial least squares

We employed partial least squares (PLS) analysis to examine the relationship between cortical centile maps within CT/SA subtypes and a range of spatial brain maps, including cognitive activation profiles, and microarchitectural features. PLS is a multivariate technique that identifies latent variables by maximizing the covariance between predictors and responses through weighted linear combinations of the original variables. For each spatial map, a loading score was calculated as the Pearson's correlation between the original map and the derived latent variables, providing a measure of its contribution to

the shared variance structure. The statistical significance of each latent variable was determined by comparing the observed covariance to a null distribution generated via 1,000 times spatial autocorrelation-preserving permutation tests¹²¹ (spin tests).

Multimodal disease epicenter

To identify the multi-level disease epicenters associated with CT/SA subtypes, we performed connectivity-based epicenter mapping across multiple phenotypic axes, including structural, functional, electrophysiological, metabolic, receptor, and genetic connectomes, as constructed by Hansen et al¹²². Disease epicenters are defined as brain regions whose normative connectivity profiles in healthy individuals spatially resemble patterns of disorder-related cortical abnormalities.

Group-level normative connectomes were constructed from multimodal neuroimaging and molecular datasets acquired in HC cohorts. Structural and functional connectomes were derived from 326 participants in the Human Connectome Project (HCP)¹²³. Structural connectivity was estimated from diffusion-weighted MRI as the number of white matter streamlines linking each pair of cortical regions. Functional connectivity was computed as pairwise Pearson's correlations between regional resting-state fMRI time series. Electrophysiological connectivity was quantified as amplitude envelope correlations between brain regions based on magnetoencephalography recordings acquired from 33 healthy HCP participants¹²³. Metabolic connectivity was estimated by correlating regional metabolic time series from 4D [¹⁸F]-fluorodeoxyglucose PET images collected in 26 healthy individuals¹²⁴. Receptor connectivity was quantified by correlating cortical regional profiles across 18 neurotransmitter receptors and transporters³⁶. Finally, genetic connectivity was derived from regional microarray expression profiles from the AHBA¹¹⁴.

For each CT/SA subtype, we computed epicenter maps by correlating its *t*-statistic map of centile scores with the normative connectivity profile of every brain region, performed separately for each modality¹²⁵. The degree of spatial correlation between the epicenter map and the *t*-statistic map was then quantified, and the statistical significance was assessed with 1,000 times spin-tests¹²¹, allowing us to infer candidate networks that may underlie disease progression.

Data availability

The MRI dataset are partially publicly available at the Adolescent Brain Cognitive Development Study (ABCD; <https://nda.nih.gov/>); ADHD-200 Sample (https://fcon_1000.projects.nitrc.org/indi/adhd200/); Alzheimer's Disease Neuroimaging Initiative (ADNI; <https://adni.loni.usc.edu/>); Age-ility Project (<https://www.nitrc.org/projects/ageility/>); Baby Connectome Project (BCP; <https://nda.nih.gov/>); Brain Genomics Superstruct Project (<https://www.neuroinfo.org/gsp/>); Calgary Preschool MRI Dataset (<https://osf.io/axz5r/>); Cambridge Centre for Ageing and Neuroscience Dataset (Cam-CAN; <https://cam-can.mrc-cbu.cam.ac.uk/dataset/>); Chinese Color Nest Project (<https://www.scidb.cn/en/detail?dataSetId=c81f0e90a51b4cfca348ce4da6ca734e>); Chinese Human Connectome Project (<https://www.scidb.cn/en/detail?dataSetId=f512d085f3d3452a9b14689e9997ca94>); Cincinnati MR Imaging of Neurodevelopment (<https://atlaslongitudinaldatasets.ac.uk/datasets/c-mind>); Consortium for Reliability and Reproducibility (CoRR; https://fcon_1000.projects.nitrc.org/indi/CoRR/html/); Dallas Lifespan Brain Study (https://fcon_1000.projects.nitrc.org/indi/retro/dlbs.html); Developing Human Connectome Project (dHCP; <http://www.developingconnectome.org/data-release/second-data-release/>); University of North Carolina Early Brain Development Study (<https://www.med.unc.edu/psych/research/psychiatry-department-research-programs/early-brain-development-research/>); Function BIRN Phase II Multi-site fMRI Study (<http://www.nbirn.net/Resources/Downloads>);

Healthy Brain Network (https://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/); Human Connectome Project (HCP; <https://www.humanconnectome.org/>); Lifespan Human Connectome Project (<https://nda.nih.gov/>); Nathan Kline Institute-Rockland Sample (NKI-RS; https://fcon_1000.projects.nitrc.org/indi/pro/nki.html); Neuroscience in Psychiatry Network (NSPN) Dataset (<https://nspn.org.uk/>); Open Access Series of Imaging Studies (OASIS; <https://sites.wustl.edu/oasisbrains/>); Pediatric Imaging, Neurocognition, and Genetics Study (PING; <http://pingstudy.ucsd.edu/>); Pixar Dataset (<https://openfmri.org/dataset/ds000228/>); Philadelphia Neurodevelopmental Cohort (PNC; <https://www.med.upenn.edu/bbl/philadelphianeurodevelopmentalcohort.html>); Queensland Twin Adolescent Brain Project (<https://openneuro.org/datasets/ds004146/versions/1.0.4>); Strategic Research Program for Brain Sciences MRI Dataset (SRPBS; <https://bicr-resource.atr.jp/srpbsopen/>); OpenfMRI database ds000115 (<https://openfmri.org/dataset/ds000115/>); SchizConnect Project (<https://schizconnect.org/>), incorporating datasets such as BrainGluSchi, COBRE, MCICShare, and NMorphCH; Southwest University Adult Lifespan Dataset (SALD; http://fcon_1000.projects.nitrc.org/indi/retro/sald.html); Southwest University Longitudinal Imaging Multimodal Brain Data Repository (http://fcon_1000.projects.nitrc.org/indi/retro/southwestuni_qiu_index.html); UK Biobank Brain Imaging Dataset (<https://www.ukbiobank.ac.uk/>); Growing Up in Singapore Towards healthy Outcomes (GUSTO; <https://www.gusto.sg/>); Autism Brain Imaging Data Exchange (ABIDE; https://fcon_1000.projects.nitrc.org/indi/abide/); and Shanghai Autism Early Development Cohort (SAED; <https://pmc.ncbi.nlm.nih.gov/articles/PMC9723093/>). Microarchitectural maps and multimodal normative connectomes are available from the Network Neuroscience Lab (<https://github.com/netneurolab>). Mitochondrial profiles can be accessed via NeuroVault (<https://neurovault.org/collections/16418/>), and disease abnormality maps are available through the ENIGMA Toolbox (<https://github.com/MICA-MNI/ENIGMA>).

Code availability

The code and resources used in this study are all publicly available, including Freesurfer (<https://surfer.nmr.mgh.harvard.edu>), iBEAT-V2 (<https://github.com/iBEAT-V2/iBEAT-V2.0-Docker>), MRIQC (<https://github.com/nipreps/mriqc>), FSQC (<https://github.com/Deep-MI/fsqc>), normative modeling (<https://github.com/brainchart/Lifespan>), categorical community detection (<https://github.com/GenLouvain/GenLouvain>), statistical analysis (<https://scipy.org/>), PLINK (<https://www.cog-genomics.org/plink/2.0/>), PRS (<https://github.com/getian107/PRScsx>), partial least squares analysis (<https://github.com/netneurolab/pypyls>), epicenter mapping (<https://github.com/MICA-MNI/ENIGMA>), spin permutation (<https://github.com/spin-test/spin-test>), and enrichment analysis (<https://metascape.org>). Medical icons used in the schematic figure were obtained from Servier Medical Art (<https://smart.servier.com>). Brain surface visualizations were generated using netneurolab (<https://github.com/netneurolab/netneurolab>), and data visualizations were created using seaborn (<https://seaborn.pydata.org>), matplotlib (<https://matplotlib.org>), wordcloud (https://amueller.github.io/word_cloud/), and ggplot2 (<https://ggplot2.tidyverse.org>).

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Author contributions

F.L., M.C., L.L.S., Y.H., C.J.D., and H.H. designed the study. M.C. and F.L supervised the project. C.J.D., L.L.S., X.Y.L. and M.R.X. conducted preprocessing and quality control. C.J.D. conducted analyses and visualizations. C.J.D. wrote and M.C., L.L.S., Y.H., W.Z., and B.S. edited the manuscript. All other authors contributed substantially to the conception of the work, or to data acquisition, analysis, or interpretation.

Competing interests

The authors have declared that no competing interest exists.

References

1. Lord, C., Elsabbagh, M., Baird, G. & Veenstra-Vanderweele, J. Autism spectrum disorder. *Lancet* **392**, 508-520 (2018).
2. Zeidan, J., *et al.* Global prevalence of autism: A systematic review update. *Autism Res* **15**, 778-790 (2022).
3. Shan, X., *et al.* Mapping the Heterogeneous Brain Structural Phenotype of Autism Spectrum Disorder Using the Normative Model. *Biol Psychiatry* **91**, 967-976 (2022).
4. Hong, S.J., Valk, S.L., Di Martino, A., Milham, M.P. & Bernhardt, B.C. Multidimensional Neuroanatomical Subtyping of Autism Spectrum Disorder. *Cereb Cortex* **28**, 3578-3588 (2018).
5. Buch, A.M., *et al.* Molecular and network-level mechanisms explaining individual differences in autism spectrum disorder. *Nat Neurosci* **26**, 650-663 (2023).
6. Litman, A., *et al.* Decomposition of phenotypic heterogeneity in autism reveals underlying genetic programs. *Nat Genet* **57**, 1611-1619 (2025).
7. Zhang, X., *et al.* Polygenic and developmental profiles of autism differ by age at diagnosis. *Nature* **646**, 1146-1155 (2025).
8. Velmeshev, D., *et al.* Single-cell genomics identifies cell type-specific molecular changes in autism. *Science* **364**, 685-689 (2019).
9. Gandal, M.J., *et al.* Broad transcriptomic dysregulation occurs across the cerebral cortex in ASD. *Nature* **611**, 532-539 (2022).
10. Aglinskas, A., Hartshorne, J.K. & Anzellotti, S. Contrastive machine learning reveals the structure of neuroanatomical variation within autism. *Science* **376**, 1070-1074 (2022).
11. Grasby, K.L., *et al.* The genetic architecture of the human cerebral cortex. *Science* **367** (2020).
12. van Rooij, D., *et al.* Cortical and Subcortical Brain Morphometry Differences Between Patients With Autism Spectrum Disorder and Healthy Individuals Across the Lifespan: Results From the ENIGMA ASD Working Group. *Am J Psychiatry* **175**, 359-369 (2018).
13. Ecker, C. & Murphy, D. Neuroimaging in autism--from basic science to translational research. *Nat Rev Neurol* **10**, 82-91 (2014).
14. Pretzsch, C.M., *et al.* Patterns of Brain Maturation in Autism and Their Molecular Associations. *JAMA Psychiatry* **81**, 1253-1264 (2024).
15. Zielinski, B.A., *et al.* Longitudinal changes in cortical thickness in autism and typical development. *Brain* **137**, 1799-1812 (2014).
16. Duan, K., *et al.* Differences in regional brain structure in toddlers with autism are related to future language outcomes. *Nat Commun* **15**, 5075 (2024).
17. Khundrakpam, B.S., Lewis, J.D., Kostopoulos, P., Carbonell, F. & Evans, A.C. Cortical Thickness Abnormalities in Autism Spectrum Disorders Through Late Childhood, Adolescence, and Adulthood: A Large-Scale MRI Study. *Cereb Cortex* **27**, 1721-1731 (2017).
18. Bethlehem, R.A.I., *et al.* Brain charts for the human lifespan. *Nature* **604**, 525-533 (2022).
19. Hazlett, H.C., *et al.* Early brain development in infants at high risk for autism spectrum disorder. *Nature* **542**, 348-351 (2017).
20. Sun, L., *et al.* Human lifespan changes in the brain's functional connectome. *Nat Neurosci* **28**, 891-901 (2025).
21. Di Martino, A., *et al.* The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol Psychiatry* **19**, 659-667 (2014).
22. Di Martino, A., *et al.* Enhancing studies of the connectome in autism using the autism brain imaging data exchange II. *Sci Data* **4**, 170010 (2017).
23. Dai, Y., *et al.* Shanghai Autism Early Development: An Integrative Chinese ASD Cohort. *Neurosci Bull* **38**, 1603-

1607 (2022).

24. Zhang, J., *et al.* Cohort profile: the Shanghai Birth Cohort. *Int J Epidemiol* **48**, 21-21g (2019).
25. Wang, L., *et al.* iBEAT V2.0: a multisite-applicable, deep learning-based pipeline for infant cerebral cortical surface reconstruction. *Nat Protoc* **18**, 1488-1509 (2023).
26. Dale, A.M., Fischl, B. & Sereno, M.I. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* **9**, 179-194 (1999).
27. Desikan, R.S., *et al.* An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* **31**, 968-980 (2006).
28. Stasinopoulos, D.M. & Rigby, R.A. Generalized Additive Models for Location Scale and Shape (GAMLSS) in R. *Journal of Statistical Software* **23** (2007).
29. Borghi, E., *et al.* Construction of the World Health Organization child growth standards: selection of methods for attained growth curves. *Stat Med* **25**, 247-265 (2006).
30. Mucha, P.J., Richardson, T., Macon, K., Porter, M.A. & Onnela, J.P. Community structure in time-dependent, multiscale, and multiplex networks. *Science* **328**, 876-878 (2010).
31. Makowski, C., *et al.* Discovery of genomic loci of the human cerebral cortex using genetically informed brain atlases. *Science* **375**, 522-528 (2022).
32. Grove, J., *et al.* Identification of common genetic risk variants for autism spectrum disorder. *Nat Genet* **51**, 431-444 (2019).
33. Poldrack, R.A., *et al.* The cognitive atlas: toward a knowledge foundation for cognitive neuroscience. *Front Neuroinform* **5**, 17 (2011).
34. Luppi, A.I., *et al.* Contributions of network structure, chemoarchitecture and diagnostic categories to transitions between cognitive topographies. *Nat Biomed Eng* **8**, 1142-1161 (2024).
35. Shafiei, G., *et al.* Neurophysiological signatures of cortical micro-architecture. *Nat Commun* **14**, 6000 (2023).
36. Hansen, J.Y., *et al.* Mapping neurotransmitter systems to the structural and functional organization of the human neocortex. *Nat Neurosci* **25**, 1569-1581 (2022).
37. Mosharov, E.V., *et al.* A human brain map of mitochondrial respiratory capacity and diversity. *Nature* **641**, 749-758 (2025).
38. Markello, R.D., *et al.* neuromaps: structural and functional interpretation of brain maps. *Nat Methods* **19**, 1472-1479 (2022).
39. Alexander-Bloch, A.F., *et al.* On testing for spatial correspondence between maps of human brain structure and function. *Neuroimage* **178**, 540-551 (2018).
40. Craig, A.D. Significance of the insula for the evolution of human awareness of feelings from the body. *Ann N Y Acad Sci* **1225**, 72-82 (2011).
41. Damasio, A.R. The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philos Trans R Soc Lond B Biol Sci* **351**, 1413-1420 (1996).
42. Uddin, L.Q. Salience processing and insular cortical function and dysfunction. *Nat Rev Neurosci* **16**, 55-61 (2015).
43. Uddin, L.Q., *et al.* Salience network-based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry* **70**, 869-879 (2013).
44. Nomi, J.S., Molnar-Szakacs, I. & Uddin, L.Q. Insular function in autism: Update and future directions in neuroimaging and interventions. *Prog Neuropsychopharmacol Biol Psychiatry* **89**, 412-426 (2019).
45. Sydnor, V.J., *et al.* Neurodevelopment of the association cortices: Patterns, mechanisms, and implications for psychopathology. *Neuron* **109**, 2820-2846 (2021).
46. Lui, J.H., Hansen, D.V. & Kriegstein, A.R. Development and evolution of the human neocortex. *Cell* **146**, 18-36

(2011).

47. Cadwell, C.R., Bhaduri, A., Mostajo-Radji, M.A., Keefe, M.G. & Nowakowski, T.J. Development and Arealization of the Cerebral Cortex. *Neuron* **103**, 980-1004 (2019).
48. Wallace, J.L. & Pollen, A.A. Human neuronal maturation comes of age: cellular mechanisms and species differences. *Nat Rev Neurosci* **25**, 7-29 (2024).
49. Ball, G., *et al.* Molecular signatures of cortical expansion in the human foetal brain. *Nat Commun* **15**, 9685 (2024).
50. Robertson, C.E. & Baron-Cohen, S. Sensory perception in autism. *Nat Rev Neurosci* **18**, 671-684 (2017).
51. Cerliani, L., *et al.* Increased Functional Connectivity Between Subcortical and Cortical Resting-State Networks in Autism Spectrum Disorder. *JAMA Psychiatry* **72**, 767-777 (2015).
52. Hwang, G., *et al.* Assessment of Neuroanatomical Endophenotypes of Autism Spectrum Disorder and Association With Characteristics of Individuals With Schizophrenia and the General Population. *JAMA Psychiatry* **80**, 498-507 (2023).
53. Jia, T., *et al.* Hierarchical Neurocognitive Model of Externalizing and Internalizing Comorbidity. *Res Sq* (2025).
54. Duan, X., Shan, X., Uddin, L.Q. & Chen, H. The Future of Disentangling the Heterogeneity of Autism With Neuroimaging Studies. *Biol Psychiatry* **97**, 428-438 (2025).
55. Pagani, M., *et al.* mTOR-related synaptic pathology causes autism spectrum disorder-associated functional hyperconnectivity. *Nat Commun* **12**, 6084 (2021).
56. Sato, M., Nakai, N., Fujima, S., Choe, K.Y. & Takumi, T. Social circuits and their dysfunction in autism spectrum disorder. *Mol Psychiatry* **28**, 3194-3206 (2023).
57. Velikonja, T., Fett, A.K. & Velthorst, E. Patterns of Nonsocial and Social Cognitive Functioning in Adults With Autism Spectrum Disorder: A Systematic Review and Meta-analysis. *JAMA Psychiatry* **76**, 135-151 (2019).
58. D'Cruz, A.M., *et al.* Reduced behavioral flexibility in autism spectrum disorders. *Neuropsychology* **27**, 152-160 (2013).
59. Woolgar, A., Duncan, J., Manes, F. & Fedorenko, E. The multiple-demand system but not the language system supports fluid intelligence. *Nat Hum Behav* **2**, 200-204 (2018).
60. Duncan, J., *et al.* A neural basis for general intelligence. *Science* **289**, 457-460 (2000).
61. Burgaleta, M., Johnson, W., Waber, D.P., Colom, R. & Karama, S. Cognitive ability changes and dynamics of cortical thickness development in healthy children and adolescents. *Neuroimage* **84**, 810-819 (2014).
62. Musliner, K.L., *et al.* Association of Polygenic Liabilities for Major Depression, Bipolar Disorder, and Schizophrenia With Risk for Depression in the Danish Population. *JAMA Psychiatry* **76**, 516-525 (2019).
63. Grotzinger, A.D., *et al.* Mapping the genetic landscape across 14 psychiatric disorders. *Nature* **649**, 406-415 (2026).
64. Gordon, A., *et al.* Developmental convergence and divergence in human stem cell models of autism. *Nature* (2026).
65. Estes, M.L. & McAllister, A.K. Immune mediators in the brain and peripheral tissues in autism spectrum disorder. *Nat Rev Neurosci* **16**, 469-486 (2015).
66. Hughes, H.K., Moreno, R.J. & Ashwood, P. Innate immune dysfunction and neuroinflammation in autism spectrum disorder (ASD). *Brain Behav Immun* **108**, 245-254 (2023).
67. Lord, C., *et al.* Autism spectrum disorder. *Nat Rev Dis Primers* **6**, 5 (2020).
68. Paulsen, B., *et al.* Autism genes converge on asynchronous development of shared neuron classes. *Nature* **602**, 268-273 (2022).
69. Kuo, S.S., *et al.* Developmental Variability in Autism Across 17 000 Autistic Individuals and 4000 Siblings Without an Autism Diagnosis: Comparisons by Cohort, Intellectual Disability, Genetic Etiology, and Age at Diagnosis.

JAMA Pediatr **176**, 915-923 (2022).

70. Hirota, T. & King, B.H. Autism Spectrum Disorder: A Review. *JAMA* **329**, 157-168 (2023).
71. Bernhardt, B.C., Valk, S.L., Hong, S.J., Soulieres, I. & Mottron, L. Autism-related shifts in the brain's information processing hierarchy. *Trends Cogn Sci* **29**, 942-955 (2025).
72. Bullmore, E. & Sporns, O. The economy of brain network organization. *Nat Rev Neurosci* **13**, 336-349 (2012).
73. Harris, J.J., Jolivet, R. & Attwell, D. Synaptic energy use and supply. *Neuron* **75**, 762-777 (2012).
74. Fotiadis, P., *et al.* Structure-function coupling in macroscale human brain networks. *Nat Rev Neurosci* **25**, 688-704 (2024).
75. Allen, N.J. & Eroglu, C. Cell Biology of Astrocyte-Synapse Interactions. *Neuron* **96**, 697-708 (2017).
76. Schafer, D.P., *et al.* Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* **74**, 691-705 (2012).
77. McNamara, N.B., *et al.* Microglia regulate central nervous system myelin growth and integrity. *Nature* **613**, 120-129 (2023).
78. Peters, K.Z., Cheer, J.F. & Tonini, R. Modulating the Neuromodulators: Dopamine, Serotonin, and the Endocannabinoid System. *Trends Neurosci* **44**, 464-477 (2021).
79. Robertson, C.E., *et al.* Global motion perception deficits in autism are reflected as early as primary visual cortex. *Brain* **137**, 2588-2599 (2014).
80. Amso, D., Haas, S., Tenenbaum, E., Markant, J. & Sheinkopf, S.J. Bottom-up attention orienting in young children with autism. *J Autism Dev Disord* **44**, 664-673 (2014).
81. Pellicano, E. The development of executive function in autism. *Autism Res Treat* **2012**, 146132 (2012).
82. Raj, A., Kuceyeski, A. & Weiner, M. A network diffusion model of disease progression in dementia. *Neuron* **73**, 1204-1215 (2012).
83. Wedeen, V.J., *et al.* The geometric structure of the brain fiber pathways. *Science* **335**, 1628-1634 (2012).
84. Khundrakpam, B., *et al.* A critical role of brain network architecture in a continuum model of autism spectrum disorders spanning from healthy individuals with genetic liability to individuals with ASD. *Mol Psychiatry* **28**, 1210-1218 (2023).
85. American Psychiatric Association, DSM-5 Task Force. (2013). Diagnostic and statistical manual of mental disorders: DSM-5™ (5th ed.). American Psychiatric Publishing, Inc.. <https://doi.org/10.1176/appi.books.9780890425596>.
86. Lord, C., *et al.* The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* **30**, 205-223 (2000).
87. Hus, V., Gotham, K. & Lord, C. Standardizing ADOS domain scores: separating severity of social affect and restricted and repetitive behaviors. *J Autism Dev Disord* **44**, 2400-2412 (2014).
88. Wang, Y., *et al.* Prenatal and postnatal exposure to organophosphate pesticides and childhood neurodevelopment in Shandong, China. *Environ Int* **108**, 119-126 (2017).
89. Wechsler, D. (2002). Wechsler preschool and primary scale of intelligence (3rd ed.). San Antonio, TX: Psychological Corporation.
90. Wechsler, D. (2003). Wechsler intelligence scale for children (4th ed.). San Antonio: The Psychological Corporation.
91. Moon, S.J., *et al.* Accuracy of the Childhood Autism Rating Scale: a systematic review and meta-analysis. *Dev Med Child Neurol* **61**, 1030-1038 (2019).
92. Bölte, S., Poustka, F. & Constantino, J.N. Assessing autistic traits: cross-cultural validation of the social responsiveness scale (SRS). *Autism Res* **1**, 354-363 (2008).
93. Esteban, O., *et al.* MRIQC: Advancing the automatic prediction of image quality in MRI from unseen sites. *PLoS*

One **12**, e0184661 (2017).

94. Purcell, S., *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* **81**, 559-575 (2007).

95. Chang, C.C., *et al.* Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7 (2015).

96. Li, L., *et al.* The ChinaMAP reference panel for the accurate genotype imputation in Chinese populations. *Cell Res* **31**, 1308-1310 (2021).

97. Demontis, D., *et al.* Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nat Genet* **55**, 198-208 (2023).

98. Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. Electronic address, a.m.e.a.u. & Major Depressive Disorder Working Group of the Psychiatric Genomics, C. Trans-ancestry genome-wide study of depression identifies 697 associations implicating cell types and pharmacotherapies. *Cell* **188**, 640-652 e649 (2025).

99. Trubetskoy, V., *et al.* Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* **604**, 502-508 (2022).

100. Strom, N.I., *et al.* Genome-wide analyses identify 30 loci associated with obsessive-compulsive disorder. *Nat Genet* **57**, 1389-1401 (2025).

101. O'Connell, K.S., *et al.* Genomics yields biological and phenotypic insights into bipolar disorder. *Nature* **639**, 968-975 (2025).

102. Friligkou, E., *et al.* Gene discovery and biological insights into anxiety disorders from a large-scale multi-ancestry genome-wide association study. *Nat Genet* **56**, 2036-2045 (2024).

103. Watson, H.J., *et al.* Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat Genet* **51**, 1207-1214 (2019).

104. Savage, J.E., *et al.* Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet* **50**, 912-919 (2018).

105. Okbay, A., *et al.* Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. *Nat Genet* **54**, 437-449 (2022).

106. Eising, E., *et al.* Genome-wide analyses of individual differences in quantitatively assessed reading- and language-related skills in up to 34,000 people. *Proc Natl Acad Sci U S A* **119**, e2202764119 (2022).

107. Wen, J., *et al.* The genetic architecture of biological age in nine human organ systems. *Nat Aging* **4**, 1290-1307 (2024).

108. Wen, J., *et al.* The genetic architecture of multimodal human brain age. *Nat Commun* **15**, 2604 (2024).

109. Hinrichs, A.S., *et al.* The UCSC Genome Browser Database: update 2006. *Nucleic Acids Res* **34**, D590-598 (2006).

110. Ge, T., Chen, C.Y., Ni, Y., Feng, Y.A. & Smoller, J.W. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat Commun* **10**, 1776 (2019).

111. Ruan, Y., *et al.* Improving polygenic prediction in ancestrally diverse populations. *Nat Genet* **54**, 573-580 (2022).

112. Zhou, Y., *et al.* Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. *Nat Commun* **10**, 1523 (2019).

113. Glasser, M.F. & Van Essen, D.C. Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. *J Neurosci* **31**, 11597-11616 (2011).

114. Hawrylycz, M.J., *et al.* An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature* **489**, 391-399 (2012).

115. Hansen, J.Y., *et al.* Local molecular and global connectomic contributions to cross-disorder cortical abnormalities. *Nat Commun* **13**, 4682 (2022).

116. Finnema, S.J., *et al.* Imaging synaptic density in the living human brain. *Sci Transl Med* **8**, 348ra396 (2016).
117. Vaishnavi, S.N., *et al.* Regional aerobic glycolysis in the human brain. *Proc Natl Acad Sci U S A* **107**, 17757-17762 (2010).
118. Hill, J., *et al.* Similar patterns of cortical expansion during human development and evolution. *Proc Natl Acad Sci U S A* **107**, 13135-13140 (2010).
119. Reardon, P.K., *et al.* Normative brain size variation and brain shape diversity in humans. *Science* **360**, 1222-1227 (2018).
120. Seidlitz, J., *et al.* Transcriptomic and cellular decoding of regional brain vulnerability to neurogenetic disorders. *Nat Commun* **11**, 3358 (2020).
121. Vasa, F. & Misić, B. Null models in network neuroscience. *Nat Rev Neurosci* **23**, 493-504 (2022).
122. Hansen, J.Y., *et al.* Integrating multimodal and multiscale connectivity blueprints of the human cerebral cortex in health and disease. *PLoS Biol* **21**, e3002314 (2023).
123. Van Essen, D.C., *et al.* The WU-Minn Human Connectome Project: an overview. *Neuroimage* **80**, 62-79 (2013).
124. Jamadar, S.D., *et al.* Simultaneous BOLD-fMRI and constant infusion FDG-PET data of the resting human brain. *Sci Data* **7**, 363 (2020).
125. Larivière, S., *et al.* The ENIGMA Toolbox: multiscale neural contextualization of multisite neuroimaging datasets. *Nat Methods* **18**, 698-700 (2021).
126. Schaefer, A., *et al.* Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cereb Cortex* **28**, 3095-3114 (2018).

Figure legends

Fig.1 | Schematic overview of the study. **a**, MRI data included in this study comprised 60,234 healthy controls (HC) and 3,117 participants with autism spectrum disorder (ASD), aggregated from 193 scanning sites after rigorous quality control. The HC cohorts collectively spanned the age range from birth to 100 years, and the ASD cohorts ranged from 1 to 62 years. Box plots show the age distribution of each cohort, colored by log-transformed sample size. **b**, Normative modeling was performed using the GAMLSS framework fitted to HC cohorts for each brain region and measure, estimating sex-stratified lifespan brain charts while controlling for batch effects. Age- and sex-normalized centile scores for cortical thickness (CT) and surface area (SA) of each ASD individual were then derived based on the lifespan normative models. **c**, A categorical multilayer community detection algorithm was applied to concatenated CT-SA inter-individual similarity matrices, yielding community assignments for each ASD participant across measures. **d**, Multi-omics analyses delineated subtype-specific biological signatures, including polygenic liability, plasma proteomics, microarchitectural features, and disease epicenters. PGSs, Polygenic scores; OR, odds ratio.

Fig.2 | Neuroanatomical subtypes in ASD. **a,b**, Neuroanatomical deviation patterns of CT and SA subtypes. Statistical significance of deviation patterns was assessed using one-sample *t*-tests with FDR correction ($p\text{-FDR} < 0.05$). **c**, Proportion of CT-SA community overlap, showing that 59.5% of ASD participants were assigned to different CT and SA subtypes. **d,e**, Age and sex distributions across CT and SA subtypes. Age differences between subtypes were evaluated using one-way analysis of variance (ANOVA), with pairwise comparisons performed using Welch's *t*-tests. Statistical significance is indicated by stars on the boxplots ($p < 0.05$). Sex distribution differences were assessed using χ^2 tests.

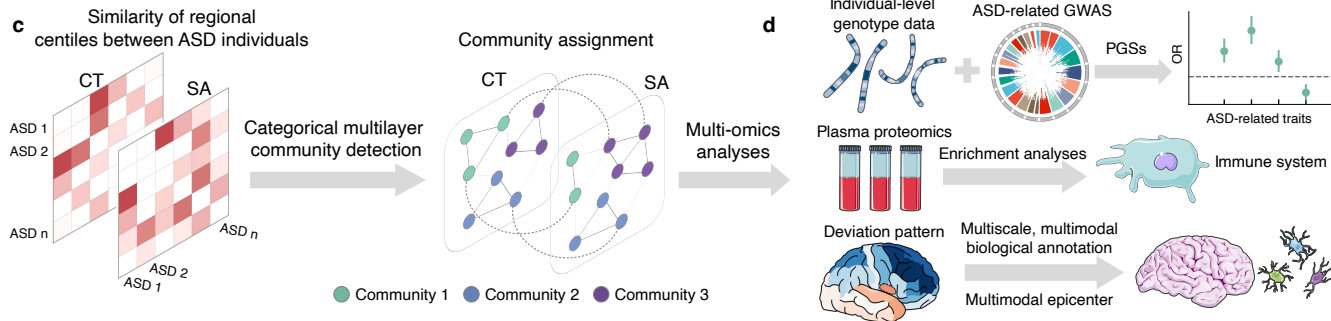
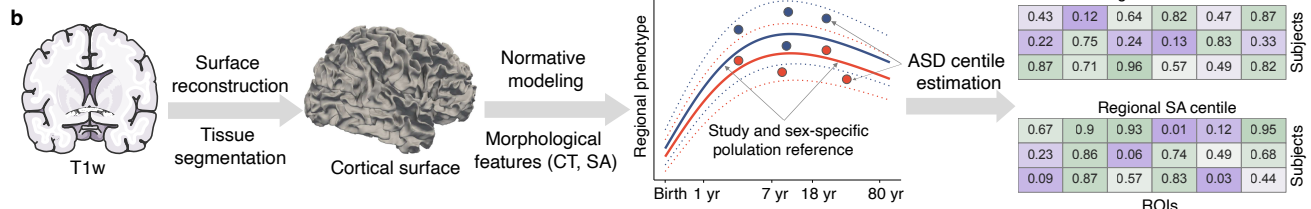
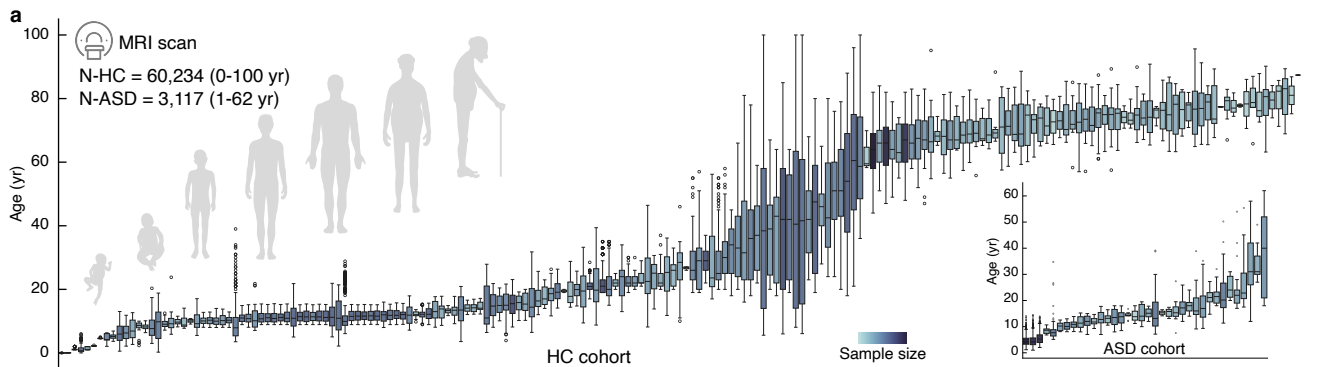
Fig.3 | Behavioral and clinical symptom characterization. **a**, Bar plots showing *F*-statistics from one-way ANOVA, with FDR correction, for z-scored behavioral scores and clinical measures across CT and SA subtypes. Variables surviving FDR correction ($p\text{-FDR} < 0.05$) are shown in deep purple, whereas those reaching nominal significance ($p < 0.05$) are indicated in light purple. **b**, Post hoc analyses (Welch's *t*-tests) of variables exhibiting significant group effects across CT subtypes. Significance levels are denoted as * $p\text{-FDR} < 0.05$; ** $p\text{-FDR} < 0.01$; *** $p\text{-FDR} < 0.001$; **** $p\text{-FDR} < 0.0001$.

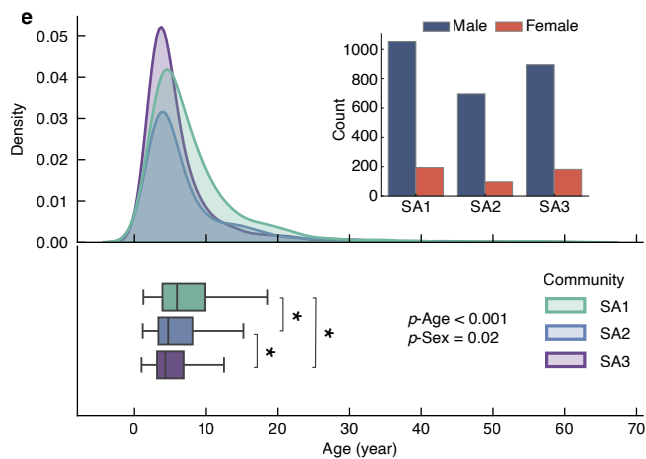
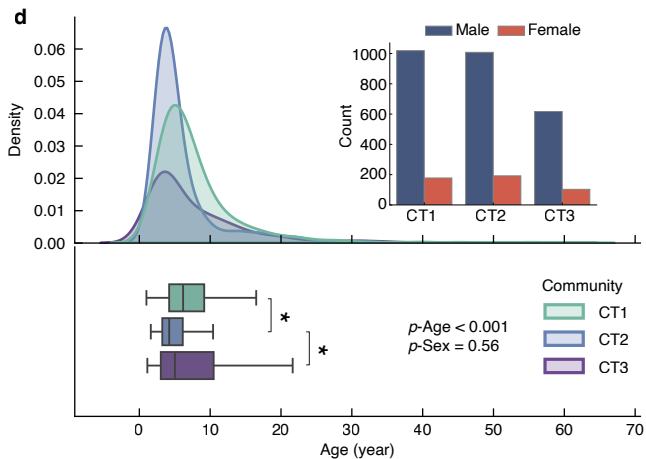
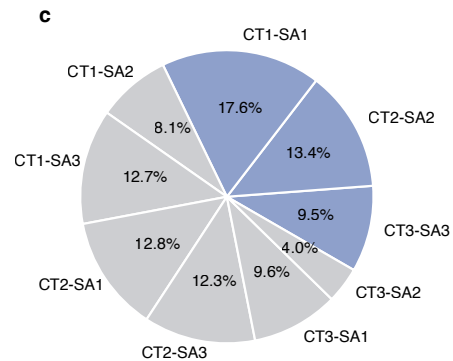
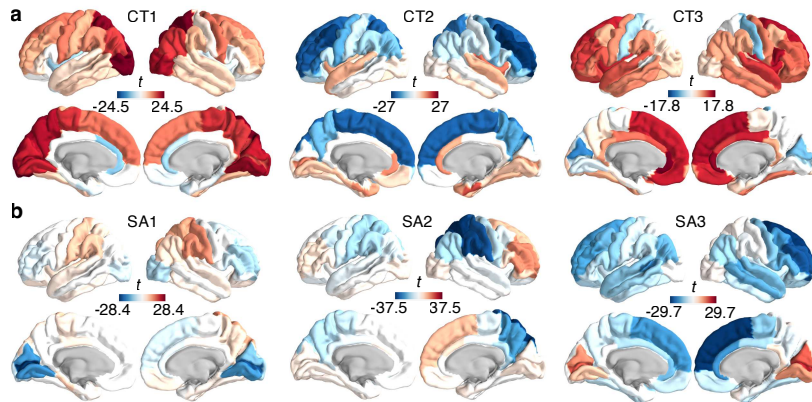
Fig. 4 | Polygenic architecture. **a**, Polygenic scores (PGSs) for ASD individuals relative to HC across ASD-related GWAS. **b**, PGSs for each CT/SA subtype compared to HC. ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; BAG, biological age gap; FC, functional connectivity. Circles indicate the odds ratio (OR) and error bars show the 95% confidence intervals. Colored circles denote significant differences.

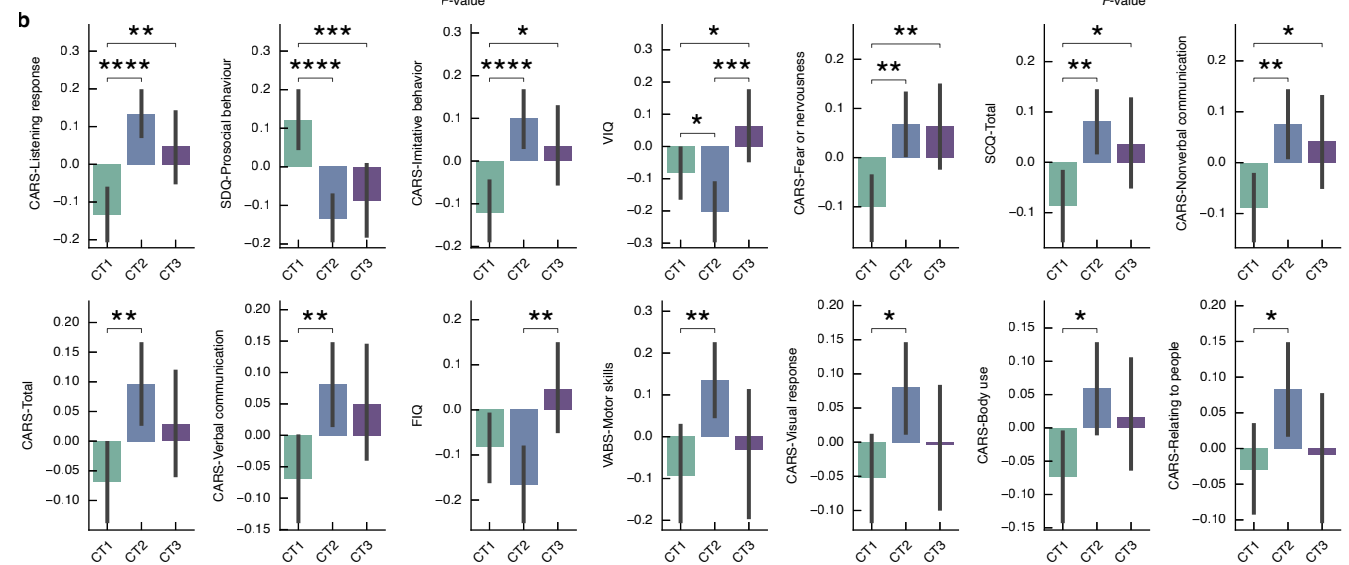
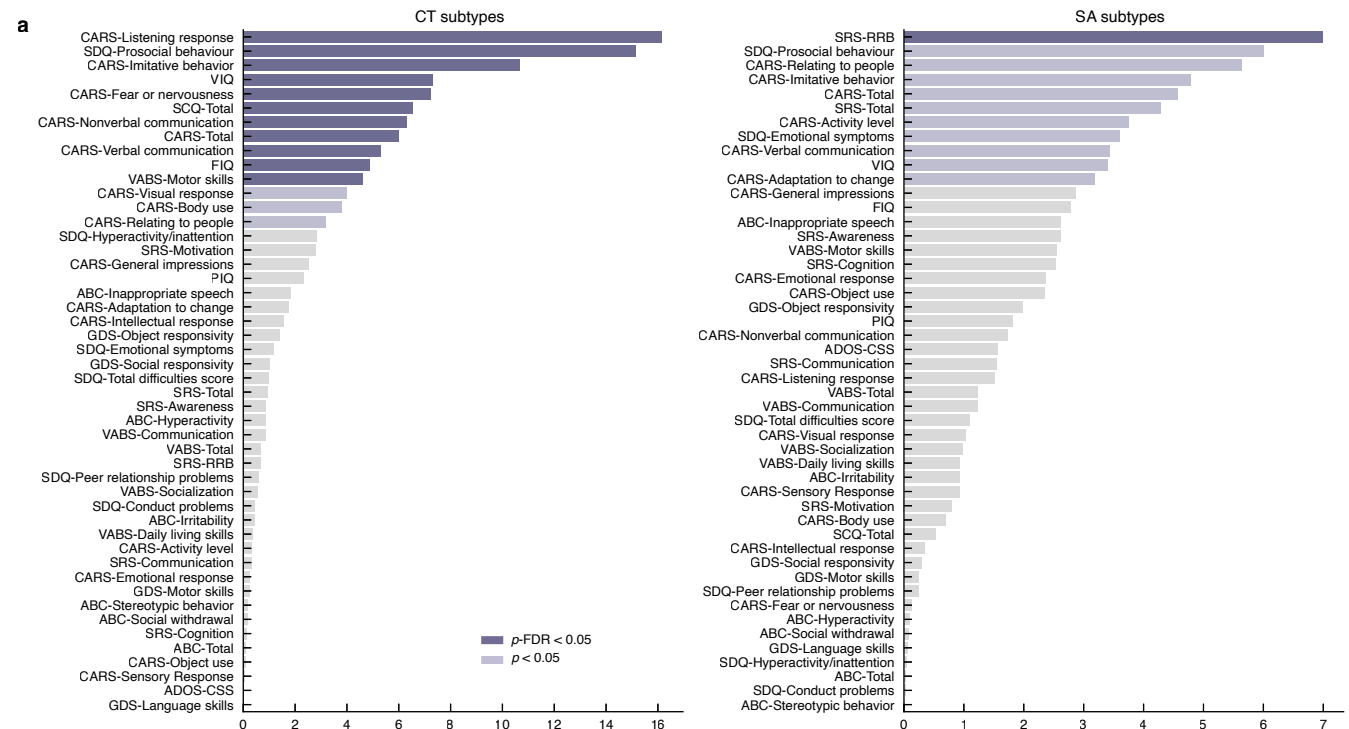
Fig. 5 | Plasma proteomic signatures. **a,b**, Differential plasma protein expression between each CT/SA subtype and HC, and across CT/SA subtypes. Each point represents a plasma protein in the volcano plots, with the three most up- or down-regulated proteins annotated. The top 15 proteins exhibiting significant differential expression among ASD subtypes are shown. **c,d**, The top five significantly enriched biological processes derived from proteins with significantly altered plasma expression. Statistical significance for comparisons between each ASD subtype and HC was assessed using Welch's *t*-test, and differences across subtypes were evaluated using one-way ANOVA.

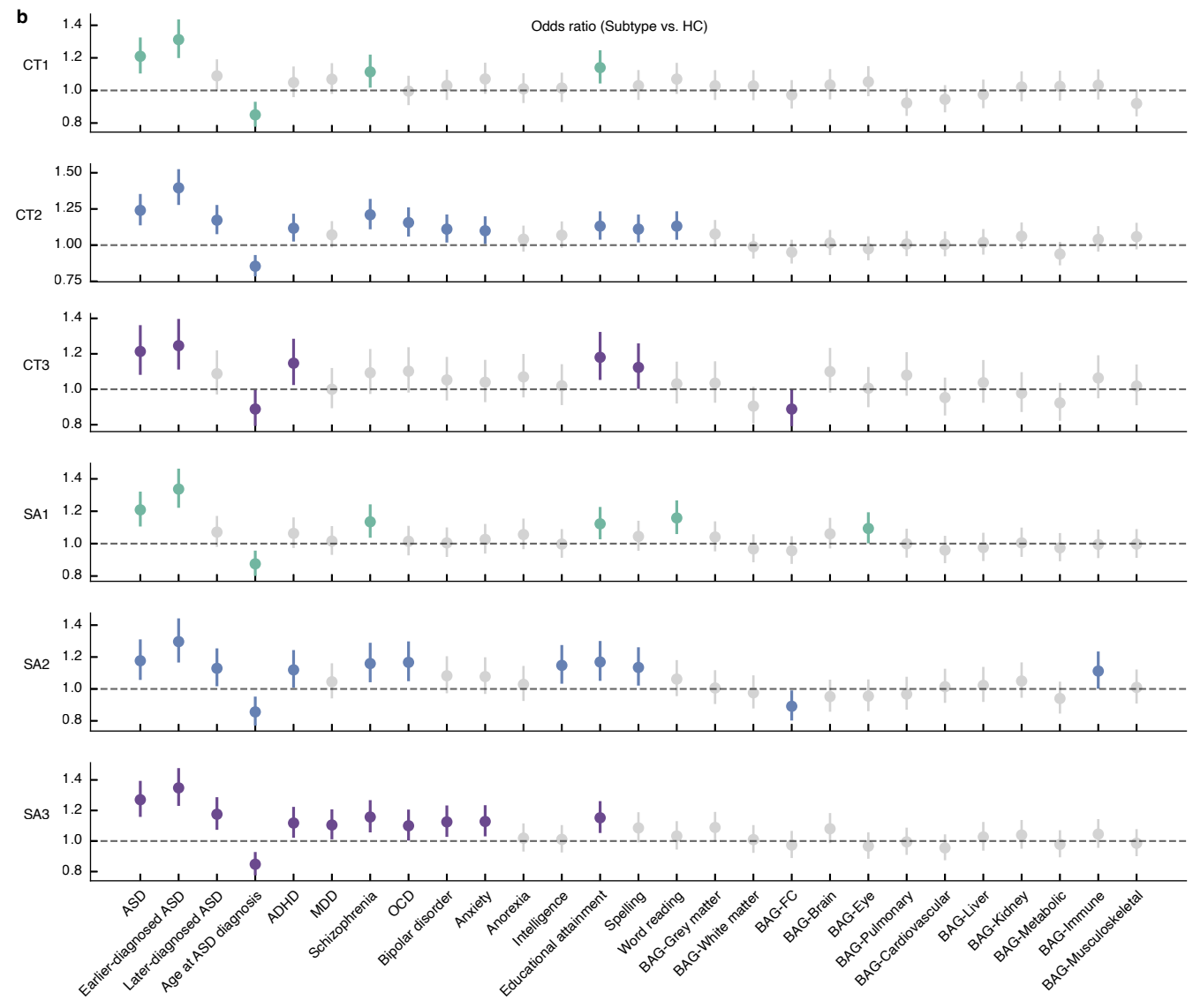
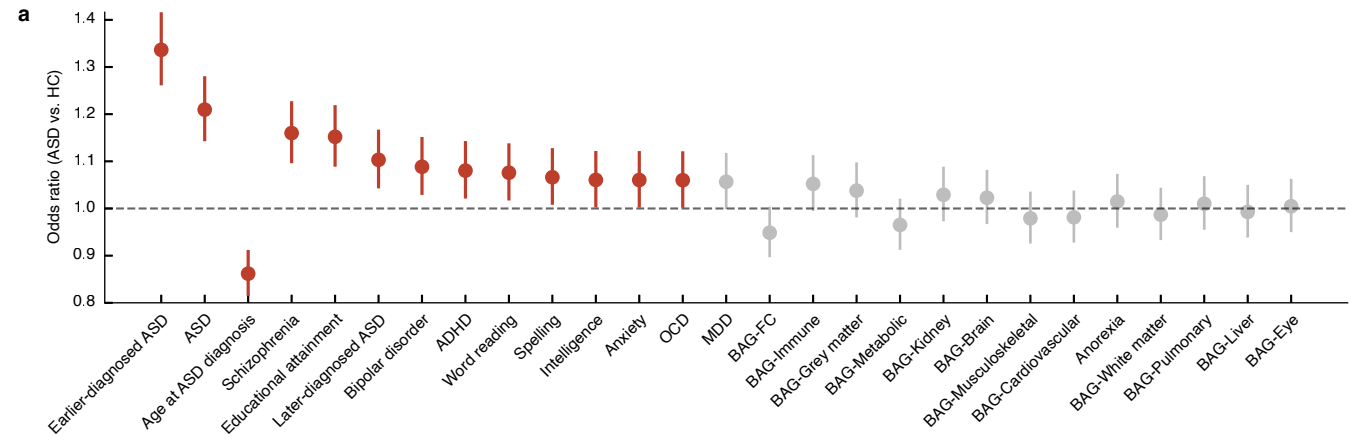
Fig.6 | Cognitive and biological annotation. **a**, PLS analysis was used to assess multivariate relationships between centile scores and cognitive processes or microarchitectural features. Latent variables are ranked by effect size, defined as the proportion of shared covariance explained by the first principal component of the PLS, and shown as yellow dots. Statistical significance was evaluated using a spatial autocorrelation-preserving null model (1,000 permutations; grey). Boxplots indicate the first, second (median), and third quartiles of the null distribution. **b**, Spatial distribution of PLS-derived scores, indexing the extent to which each brain region expresses covarying centile–feature patterns. **c,d**, PLS loadings for cognitive processes and microarchitectural features associated with the latent variables in CT and SA subtypes. Word size reflects the relative magnitude of the term loading, with red indicating positive loadings and blue indicating negative loadings. gene PC1, first principal component of gene expression; E:I ratio, excitatory-to-inhibitory receptor density ratio; Astro, astrocytes; Micro, microglia; OPC, oligodendrocyte precursor cells; Oligo, oligodendrocytes; Endo, endothelial cells; Neuro-Ex, excitatory neurons; Neuro-In, inhibitory neurons; Mitochondrial respiratory complexes I (CI), II (CII), and IV (CIV); MitoD, mitochondrial density; TRC, tissue respiratory capacity; MRC, mitochondrial respiratory capacity.

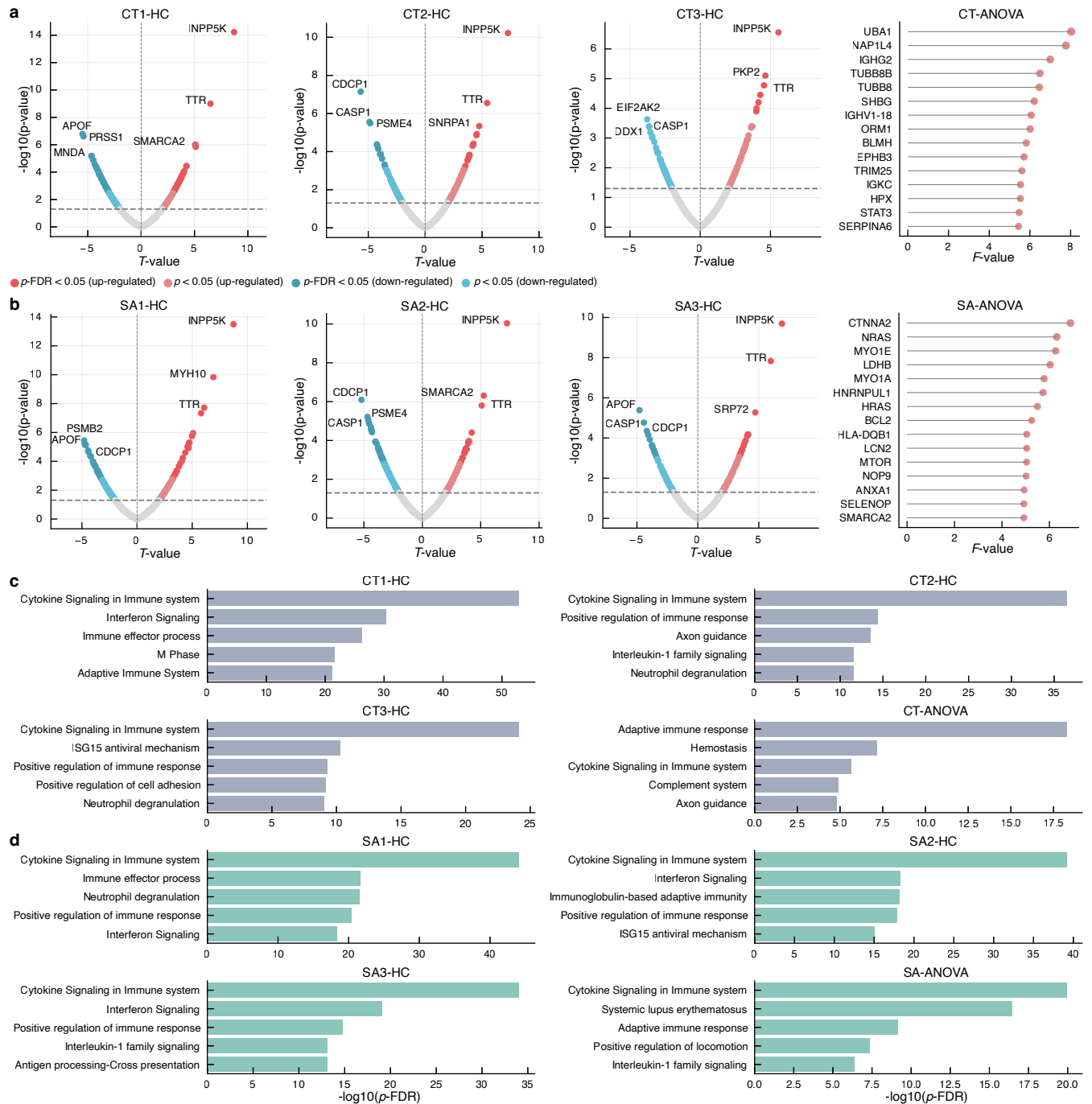
Fig.7 | Multimodal disease epicenter mapping. **a,b**, Epicenter mapping of CT and SA subtype deviation patterns across six connectomes, spanning from macroscopic structural network to microscopic gene expression network. Epicenters were defined as regions whose connection strengths showed strong correlations with deviation patterns, suggesting that cortical abnormalities may propagate from these epicentral regions to their connected neighbors. **c**, Correlations between ASD subtype deviation maps and their corresponding six epicenter maps, with significance assessed using spatial spin-permutation tests ($p\text{-spin} < 0.05$). **d**, Scatter and line-fit plots showing the strongest correlation for each subtype, with nodes colored according to the Schaefer functional networks¹²⁶. SC, structural connectivity; FC, functional connectivity; MEG, magnetoencephalography.

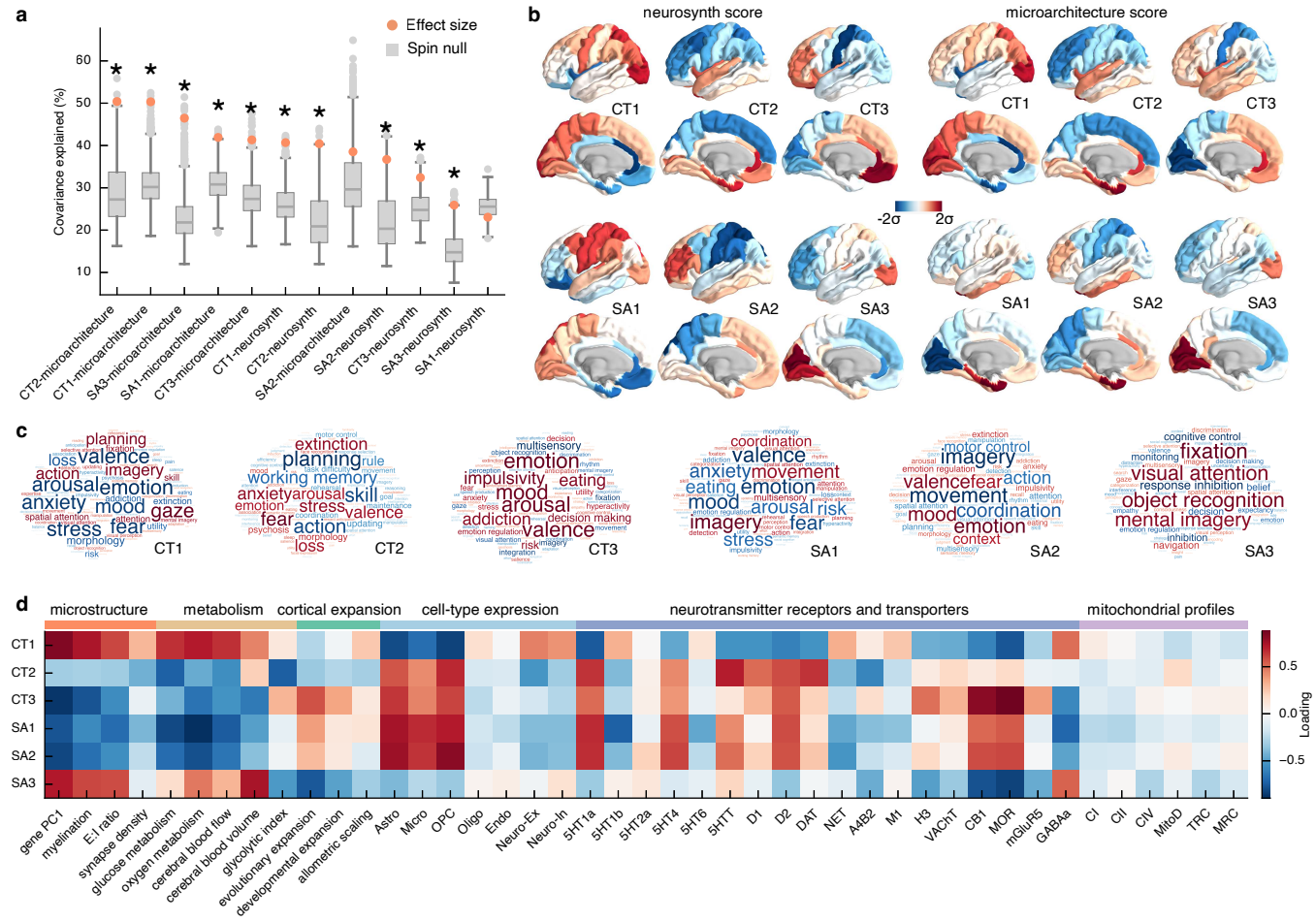


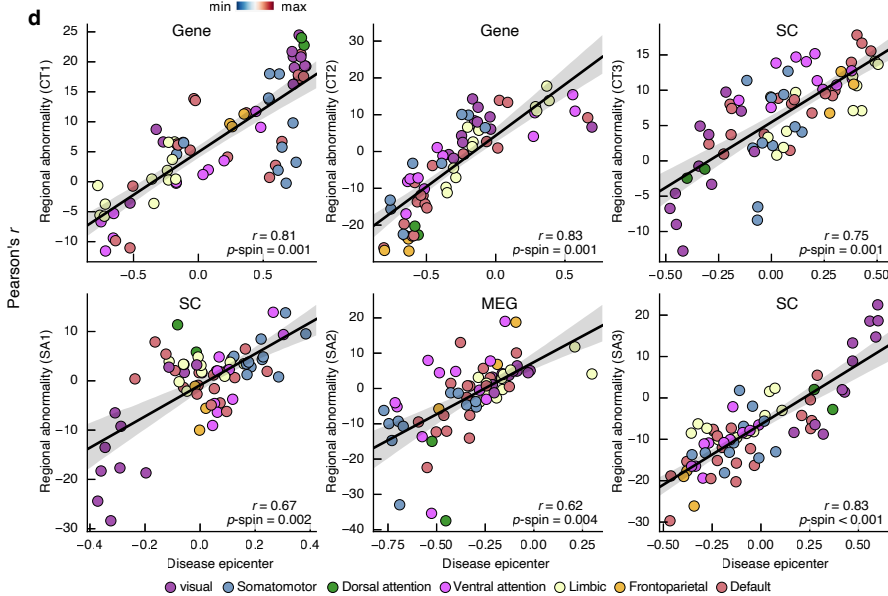
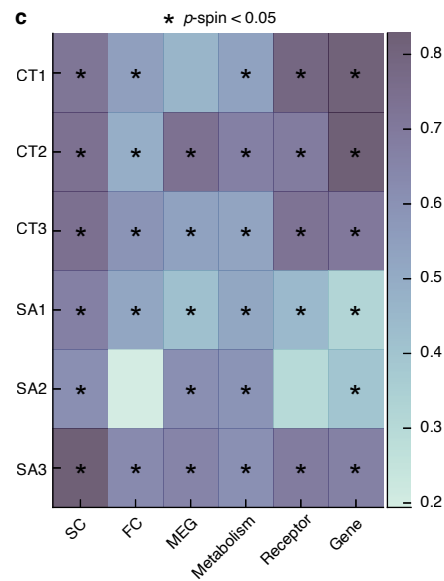
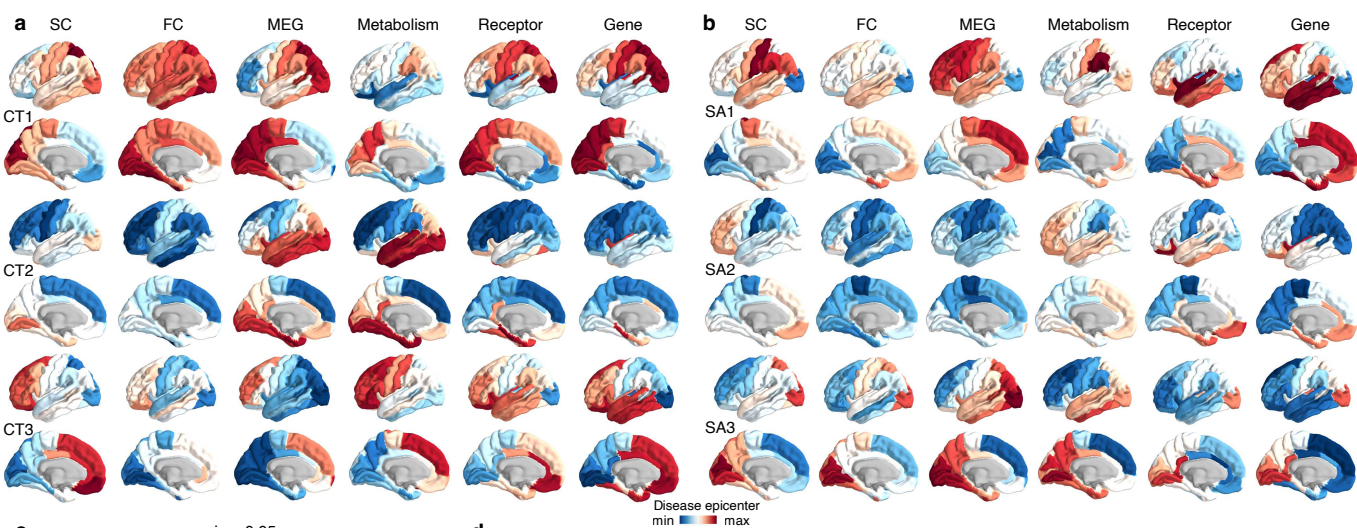












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