

## **Supplementary Materials**

### **Human cortex development is shaped by molecular and cellular brain systems**

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Supplementary Figures S1–S20.

Supplementary References.

Supplementary Tables S1–S4 are provided in a separate Excel file.

Supplementary Animations S1 and S2 are provided in separate GIF files.

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## Abbreviations:

CT	cortical thickness
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
ABA	Allen brain atlas
MNI	Montreal Neurological Institute
FDR	false-discovery rate
ABCD	Adolescent Cognitive Brain and Development
ANCOVA	analysis of covariance
ni	nuclear imaging-derived brain atlas
ce	cell marker-derived brain atlas
mr	MRI-derived brain atlas
SV2A	synaptic vesicle glycoprotein 2A
M1	muscarinic receptor 1
mGluR5	metabotropic glutamate receptor 5
5HT1a/1b/2a/4/6	serotonin receptor 1a/2a/4/6
CB	cannabinoid receptor 1
GABAa	$\gamma$ -aminobutyric acid receptor A
HDAC	histone deacetylase
5HTT	serotonin transporter
FDOPA	fluorodopa
DAT	dopamine transporter
D1/2	dopamine receptor 1/2
NMDA	N-methyl-D-aspartate glutamate receptor
GI	glycolytic index
MU	mu opioid receptor
A4B2	$\alpha$ 4 $\beta$ 2 nicotinic receptor
VAChT	vesicular acetylcholine transporter
NET	noradrenaline transporter
CBF	cerebral blood flow
CMRglu	cerebral metabolic rate of glucose
COX1	cyclooxygenase 1
H3	histamine receptor 3
TSPO	translocator protein
Ex	excitatory neurons
In	inhibitory neurons
Oligo	oligodendrocytes
Endo	endothelial cells
Micro	microglia
OPC	oligodendrocyte progenitor cells
Astro	astrocytes

## 1. Supplementary Methods and Results

### 1.1. Molecular and cellular neurobiological markers

#### 1.1.1. *Atlas sources*

As neurobiological markers of cell populations, processes, and systems potentially underlying CT changes, we collected 27 *in vivo* nuclear imaging atlases (20 neurotransmitter systems, cerebral glucose uptake, blood flow, aerobic glycolysis, synaptic density, transcriptomic activity, and two atlases capturing brain immune function), an MRI-derived atlas of cortical microstructure (T1/T2 ratio), and 21 atlases of neuronal and glial cell types generated from Allen Brain Atlas mRNA expression data based on marker genes identified in adult human brain tissue (Ext. Data Tab. 1; Ext. Data Fig. 1) (Aghourian et al., 2017; Beliveau et al., 2017; Darmanis et al., 2015; Ding et al., 2010; Dukart et al., 2018; Finnema et al., 2016; Gallezot et al., 2010, 2017; Galovic et al., 2021; Gómez et al., 2018; Hansen et al., 2022; Hawrylycz et al., 2012; Hillmer et al., 2016; Kaller et al., 2017; Kantonen et al., 2020; Kaulen et al., 2021, 2022; Kim et al., 2020; Lake et al., 2016; Lois et al., 2018; Markello et al., 2022; Naganawa et al., 2021; Normandin et al., 2015; Radhakrishnan et al., 2018; Sandiego et al., 2015; Smart et al., 2019; Vaishnavi et al., 2010; Wey et al., 2016).

#### 1.1.2. *Processing of Allen Human Brain Atlas mRNA expression data*

Regional microarray expression data were obtained from 6 post-mortem brains (1 female, age range 24.0–57.0 years, mean age  $42.50 \pm 13.38$  years) provided by the Allen Human Brain Atlas (<https://human.brain-map.org>) (Hawrylycz et al., 2012). Data were processed with the abagen toolbox (version 0.1.3; <https://github.com/rmarkello/abagen>) (Markello et al., 2021) using a 148-region surface-based atlas in fsaverage5 space (Destrieux et al., 2010).

First, microarray probes were reannotated using data provided by Arnatkevičiūtė et al. (2019); probes not matched to a valid Entrez ID were discarded. Next, probes were filtered based on their expression intensity relative to background noise (Quackenbush, 2002), such that probes with intensity less than the background in  $\geq 50\%$  of samples across donors were discarded, yielding 31,569 probes. When multiple probes indexed the expression of the same gene, we selected and used the probe with the most consistent pattern of regional variation across donors [i.e., differential stability (Hawrylycz et al., 2015)], calculated with:

$$\Delta_S(p) = \frac{1}{\binom{N}{2}} \sum_{i=1}^{N-1} \sum_{j=i+1}^N \rho[B_i(p), B_j(p)]$$

where  $p$  is Spearman's rank correlation of the expression of a single probe,  $p$ , across regions in two donors  $B_i$  and  $B_j$ , and  $N$  is the total number of donors. Here, regions correspond to the structural designations provided in the ontology from the Allen Human Brain Atlas. The MNI coordinates of tissue samples were updated to those generated via non-linear registration using the Advanced Normalization Tools (ANTs; <https://github.com/chrisfilo/alleninf>). To increase spatial coverage, tissue samples were mirrored bilaterally across the left and right hemispheres [R2018N]. Samples were assigned to brain regions by minimizing the Euclidean distance between the MNI coordinates of each sample and the nearest surface vertex. Samples where the Euclidean distance to the nearest vertex was more than 2 standard deviations above the mean distance for all samples belonging to that donor were excluded. To reduce the potential for misassignment, sample-to-region matching was constrained by hemisphere and gross structural divisions [i.e., cortex, subcortex/brainstem, and cerebellum, such that e.g., a sample in the left cortex could only be assigned to an atlas parcel in the left cortex; (Arnatkevičiūtė et al., 2019)]. All tissue samples not assigned to a brain region in the provided atlas were discarded. Inter-subject variation was addressed by normalizing tissue sample expression values across genes using a robust sigmoid function (Fulcher et al., 2013):

$$x_{norm} = \frac{1}{1 + exp - \left( \frac{(x - \langle x \rangle)}{IQR_x} \right)}$$

where  $\langle x \rangle$  is the median and  $IQR_x$  is the normalized interquartile range of the expression of a single tissue sample across genes. Normalized expression values were then rescaled to the unit interval:

$$x_{scaled} = \frac{x_{norm} - \min(x_{norm})}{\max(x_{norm}) - \min(x_{norm})}$$

Gene expression values were then normalized across tissue samples using an identical procedure. Samples assigned to the same brain region were averaged separately for each donor and then across donors, yielding a regional expression matrix with 148 rows, corresponding to brain regions, and 15,633 columns, corresponding to the retained genes.

### **1.1.3. Temporal stability of original brain atlases**

Our analyses make use of the spatial pattern present in every given brain map to draw relationships between brain maps from different sources and levels of biological organization. This pattern is encoded in the relative ranks of the metric in question across the cortex regions. To retain good interpretability of our findings, the multimodal atlases should, in the best case, show a high stability of these ranks over the adult lifespan. We tested for this by collecting the available PET maps derived from the same tracer in healthy adult samples which's mean age different from the atlases used in our main analyses (DuBois et al., 2016; Hansen et al., 2022; Kaulen et al., 2021, 2022; Rosa-Neto et al., 2005; Smith et al., 2019). Spearman correlations across cortex regions indicated a high stability ( $r \geq .77$ ) which, based on the limited data available, did not depend on sample age (Fig. S1).

### **1.1.4. Factor analyses to derive “multilevel neurobiological markers”**

We performed factor analyses to reduce multicollinearity in the following regression analyses while retaining interpretability. All unrotated factors that explained at least 1% of variance of each dataset (nuclear imaging vs. neural cell types) were retained, resulting in 10 nuclear imaging factors and 10 cell type factors (named *ni1–ni10*, and *cel–ce10*; Ext. Fig. S2). After promax rotation, nuclear imaging factors explained 90.9% and cell type factors explained 86.9% of each respective dataset (Fig. S2). Adding the MRI-derived microstructural atlas (*mrl*), 21 factors were used as “predictors” for the following analyses (Ext. Data Fig. 2).

### **1.1.5. Factor analyses validation against null data**

In sensitivity analyses, we tested if the factor solutions estimated on the original brain atlases explained significantly more variance in the original data than factor solutions estimated on permuted brain atlases. Using the same autocorrelation-preserving method as in our remaining analyses (Burt et al., 2020), we generated  $n = 10,000$  permuted brain maps. Each of these null datasets was z-standardized and used to fit a factor analysis (same settings as used in the main analyses) with  $n = 10$  factors, separately for nuclear imaging and cell types. Explained variance in the observed data was calculated as the fraction of (i) the variance in the observed dataset and (ii) the variance in each null dataset. Based on the resulting null distributions of explained variance scores, two empirical  $p$  values were calculated for the nuclear imaging and the cell type datasets. At an alpha level of  $p > .05$ , the “observed” factor analyses explained more variance in the observed

data as compared to factor analyses estimated on null data (nuclear imaging:  $p = 0.0317$ ; cell types:  $p = 0.0495$ ; Fig. S2).

## 1.2. Modeled CT data

Reference CT values across the lifespan for 148 cortex regions were extracted from the *Braincharts* normative model published by Rutherford et al. (2022) (5–90 years with 0.5-year steps; separate female and male data from approximately 58,000 subjects; 1<sup>st</sup>, 5<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, 95<sup>th</sup>, and 99<sup>th</sup> model percentile, age distribution: Fig. S3). As expected, lifespan cortical thickness development showed a general trend towards cortical thinning, with different trajectories across brain regions. While absolute values differed slightly by sex, the general trajectories and relative development were highly similar, so that we decided to average the data across sexes for all main analyses (Fig. S4A, Animation S1).

Cross-sectional colocalization analyses were based on the modeled CT data at each extracted timepoint. For analyses aiming to explain modeled longitudinal CT change patterns, we calculated timepoint-to-timepoint relative CT change of 50<sup>th</sup> percentile data within a sliding window approach (5–90-year range, 5-year length, and 1-year steps). During childhood, adolescence, and up to young adulthood, precentral and temporal gyri showed the strongest relative increase of CT while the remaining cortex showed thinning patterns. Generally, the strongest CT changes across the lifespan (mostly thinning) occurred in the first and last third of life (Fig. S4B–C).

## 1.3. Brain-regional contributions to CT association patterns

We evaluated brain-regional contributions to the overall explained CT change by calculating the residual difference for each brain atlas as the difference in prediction errors resulting from a multivariate regression with and without the brain atlas included as predictor. Generally, medial occipital, medial temporal, sensorimotor, and cingulate cortices influenced the explained CT change patterns strongly. For *ce9-In8*, the premotor cortex, cuneus, and multiple frontopolar sulci were the most influential regions. *ce3-Micro-OPC* showed a similar pattern, while *ni9-D2* showed the strongest residual differences in the middle cingulate cortex, precuneus, insula, and temporal pole. The two metabolism factors (*ni4* and *ni6*) showed less pronounced patterns with generally occipitotemporal regions having the strongest influences. The two neurobiological markers relevant for midlife CT change, *ni3-FDOPA-DAT-D1-NMDA* and *ni5-VAChT-NET*, again displayed a high relevance of lateral and medial somatosensory cortices as well as the precuneus, middle to anterior cingulate, and medial temporal regions. One marker associated to late adulthood CT

changes, *ce4-In3-In2-Astro*, displayed the strongest influences by middle and anterior cingulate cortices and medial motor areas. Fig. 3B shows the respective patterns at each marker’s maximum explained CT change, Animation S2 illustrates how the observed patterns develop longitudinally, and Fig. S8 provides an overview for the complete lifespan.

#### **1.4. Evaluation of original in comparison to dimensionality-reduced multilevel atlases**

To demonstrate that the factor-level atlases were appropriately representing the original multilevel brain atlases, we performed additional sets of (i) dominance analyses and (ii) univariate linear regressions for each factor-level atlas, using as predictors the 5 original atlases with the highest factor loadings if the absolute loading exceeded 0.3. FDR correction was performed across (i) all dominance analyses and (ii) all individual univariate regression separately.

All factors explained CT change significantly (nominal  $p < 0.05$ ). In all cases, the total explained CT change  $R^2$  peaks arising from each original atlas set occurred at the same time in life as observed for the factor-level atlases. For some factor-level atlases, we discovered that their peak contribution to explained CT change was driven by a certain original atlas, while other original atlases were of lesser relevance. For *ni3-FDOPA-DAT-D1-NMDA*, we showed that the midlife peak was mostly driven by NMDA and DAT. Other strongly loading atlases – DOPA, D1, and NET – explained more CT change before 25 and after 50 years. The contribution to early explained CT change of *ni4-GI-5HT1b-MU-A4B2* was driven by GI, capturing aerobic glycolysis. For *ni5-VACht-NET*, VACht indeed accounted for most of the CT change explained by the factor-level atlas during midlife. Furthermore, the A4B2 nicotinic receptor contributed to this factor. The relevance of *ni9-D2* for early explained CT change was indeed driven by the D2 receptor, however the D1 receptor additionally loaded on the factor and accounted for around 15% of explained early CT change. For *ce3-Micro-OPC*, the microglia distribution contributed more strongly, although explaining less CT change in comparison to other predictors. Finally, *ce5-In6-Ex2* was dominated by Ex2 (layer 3/4 granule neurons), and we observed an additional contribution of Ex3 (layer 4 granule neurons) to *ce9-In8*. Ext. Data Fig. 4 illustrates detailed results, Fig. S9 shows the peak region-wise residual differences for each original atlas.

#### **1.5. ABCD and IMAGEN cohort demographics and quality control**

We obtained single-subject CT data from the ABCD (Casey et al., 2018) and the IMAGEN (Schumann et al., 2010) cohort studies to validate our findings. Data quality was ensured based on the manual ratings included in the ABCD dataset and on FreeSurfer’s “number of surface defects”

metric. Tab. S1 lists age and sex distributions for both cohorts and each timepoint. Fig. S11 shows the quality control metric distributions.

Regarding the ABCD dataset, initially, baseline data for 11,760 subjects and 2-year follow-up data for 7,829 subjects was available. After dropping one study site without longitudinal data and subjects with missing CT data, 11,716 and 7,818 datasets were retained. Subjects with low data quality were excluded, leading to 10,697 and 6,789 subjects. 420 subjects (20 per study site) that only had baseline data were used to adapt the Braincharts reference model to the study sites and to obtain site-adjusted CT values as well as individual deviations from the 50<sup>th</sup> model percentile (Bayer et al., 2021; Rutherford et al., 2021). Only subjects with longitudinal data were included in analyses, resulting in a final dataset of  $n = 6,789$ .

Concerning the IMAGEN dataset, 4,990 observations from 2,158 subjects were initially available. For 3,975 observations from 1,528 subjects, structural MRI data was available and successfully FreeSurfer-processed. After exclusion of subjects for quality reasons, 3,732 observations from 1,522 subjects were retained. Baseline data from 160 subjects (20 per site) was used for model adaptation and these subjects were excluded from analyses completely, resulting in a dataset of  $n = 1362$  subjects to be used in analyses.

### **1.6. Generalizability of individual CT prediction models**

We asked if the prediction of individual CT change patterns was generalizable from the median predictions of the normative model to the observed single subject data, i.e., we asked if a “one-size-fits-all” approach would have performed equally well. This was done by applying the parameters of the regression models estimated to predict each subject’s *normative* CT change patterns to the same subject’s *observed* change patterns, calculating the Pearson correlation between observed and predicted CT change patterns, and comparing these model fit metrics between the different models. While these one-size-fits-all models generally exceeded the predictive performance of permuted null models, they did not provide good fit for many individuals, thus highlighting the value of our individual differences-focused approach (Fig. S16).

### **1.7. Effects of sex and site on explained CT change**

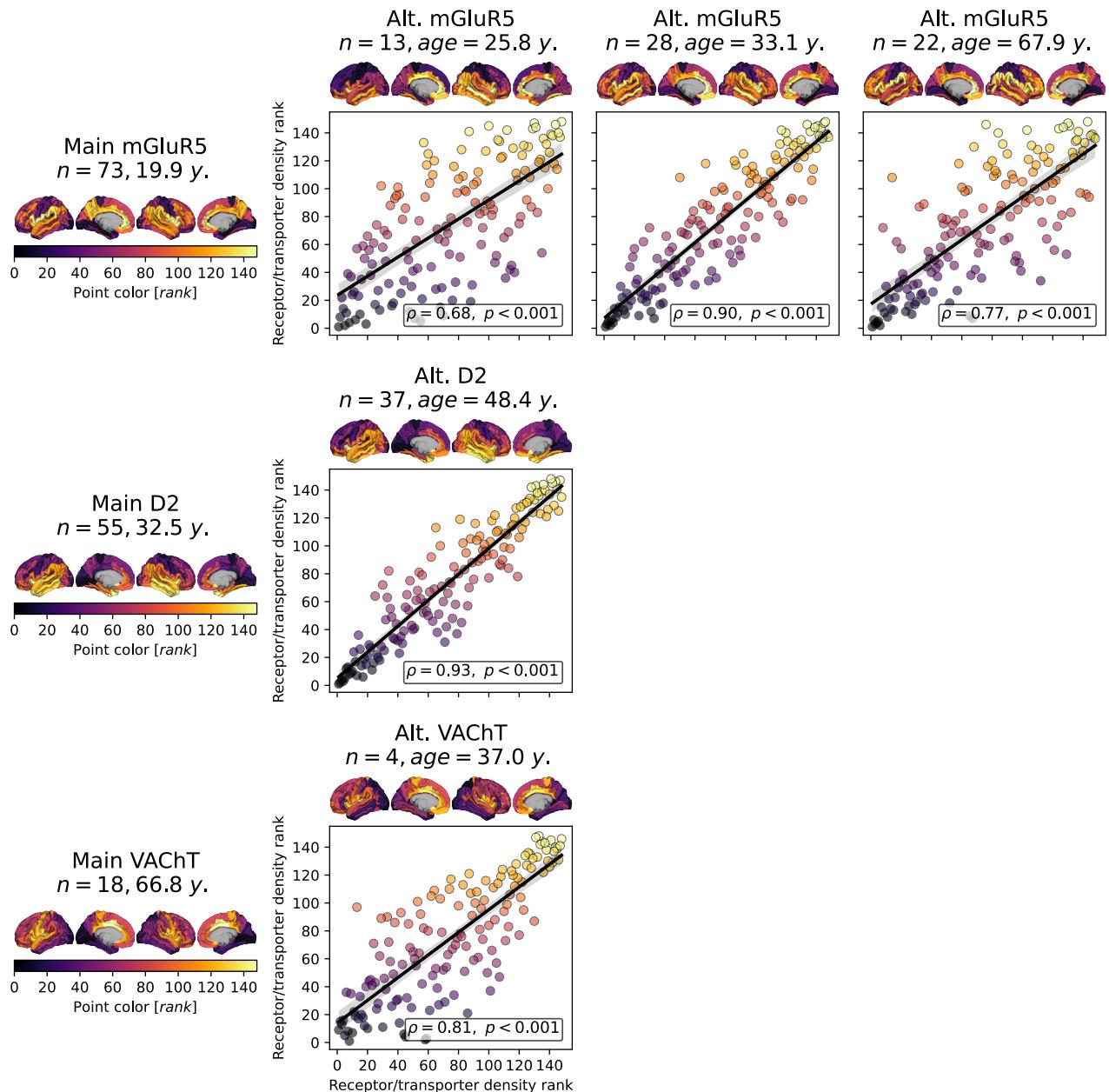
After having assessed how CT development on the single-subject level was explained from multilevel neurobiological marker, we evaluated whether the amount to which it was explained, varies with sex and study site. ANCOVA models corrected for follow-up duration showed

significantly more explained CT change in males as compared to females only in the IMAGEN dataset (timespans T0–T5 and T0–T8), but not in the ABCD data. Furthermore, we observed effects of site on explained CT change in ANCOVA models corrected for sex and follow-up duration in both datasets (all timespans). Effects of study site were also observed for cross-sectional CT as well as CT change (Tab. S2 and S3) in several cortex regions. Given that the main goal of the current analysis was to establish the feasibility of capturing associations between CT development and multilevel neurobiological markers on the individual level, clarification of the sources of sex- and site-effects will be a task for future investigations. Fig. S18 visualizes the group differences, Tabs. S2 and S3 show ANCOVA results.

### **1.8. Effects of reference model predictive performance, subject-level deviations, and data quality on explained CT change**

We conducted correlational analyses to provide general indications of which factors influenced the extents to which CT change was explained in single-subject data. First, CT change patterns of subjects who had more “normative” CT patterns at *baseline* (i.e., stronger correlation between observed and Braincharts-predicted baseline CT) were not consistently better explained. In contrast, subjects whose CT change patterns were more in line with the *change* patterns predicted by the Braincharts model showed higher explained CT change. Similarly, while we did not observe consistent relationships between metrics capturing how a subject deviated from the model-predictions (count of deviation Z scores > 2 and average absolute Z scores) and explained CT change, the longitudinal change in deviation metrics showed an association in all IMAGEN timespans: As expected, most subjects did not show strong changes in their deviations between timepoints, but subjects who showed *more or stronger deviations* at follow-up as compared to baseline tended towards *more explained CT change*. Whether such patterns could represent a potentially pathophysiological involvement of a certain neurobiological marker in neurodevelopment remains to be investigated. Finally, we observed that less CT change was explained in subjects with more surface defects (i.e., worse reconstruction quality) at follow-up (ABCD and IMAGEN) or at baseline (ABCD only). Fig. S19 shows the reported association patterns and provides Spearman correlation statistics.

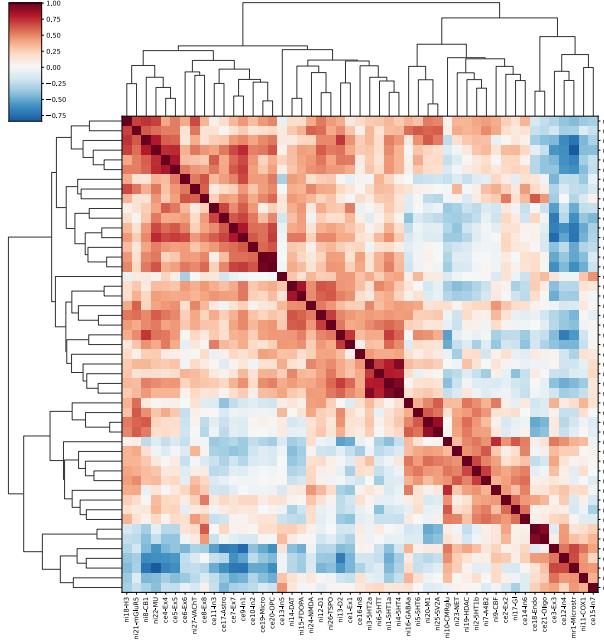
## 2. Supplementary Figures



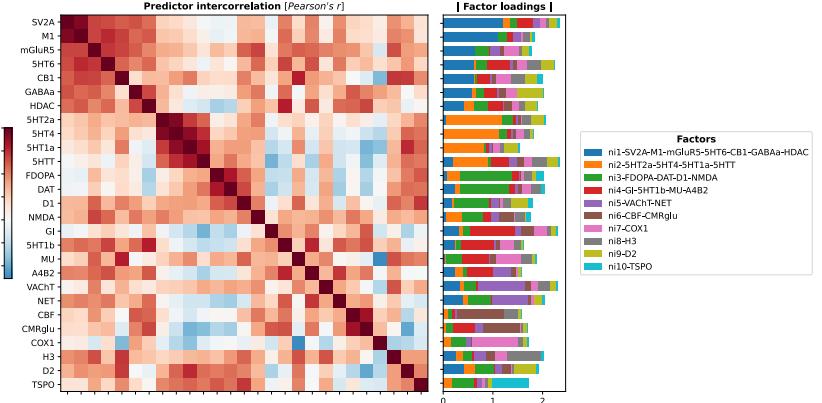
**Fig. S1: Stability of regional PET atlas ranks throughout the adult lifespan**

Comparison of PET atlases derived from independent healthy adult samples. We included all available PET atlases that used the same tracer but differed in regards to mean sample age, which resulted in three tracers for the glutamatergic, dopaminergic, and cholinergic systems. This analysis aimed to demonstrate, using the limited data available, that the *ranks* of regional tracer density across the cortex are stable during the adult lifespan. **Left side and y-axes:** Atlases used in the main analyses of this study (Aghourian et al., 2017; Sandiego et al., 2015; Smart et al., 2019). **Scatter points** are colored according to the regional values. **Surface plots on top of each panel and x-axes:** Alternative atlases (DuBois et al., 2016; Hansen et al., 2022; Kaulen et al., 2021, 2022; Rosa-Neto et al., 2005; Smith et al., 2019). **Statistics:** Spearman correlations and parametric p-values. **Abbreviations:** Alt. = alternative, y. = years, mGluR5 = metabotropic glutamate receptor 5, D2 = dopamine receptor 2, VACHT = vesicular acetylcholine receptor.

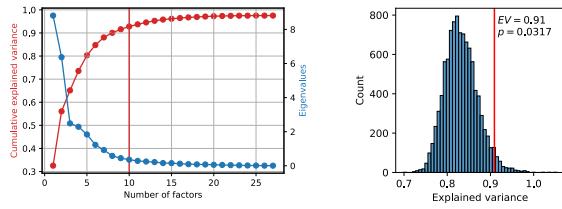
### A: Original atlas intercorrelation



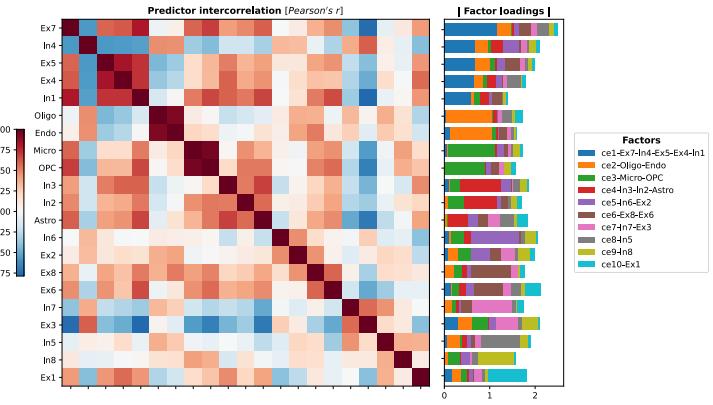
### D: Factor loadings: nuclear imaging



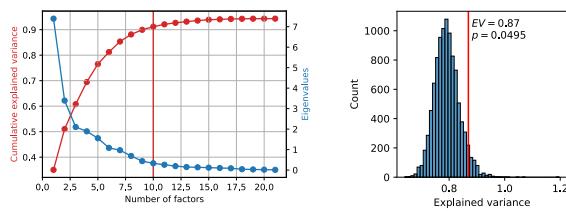
### B: Explained variance: nuclear imaging



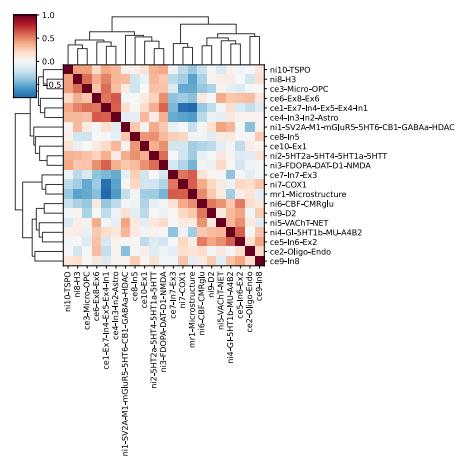
### E: Factor loadings: mRNA cell type markers



### C: Explained variance: mRNA cell type markers



### F: Combined factor-level atlas intercorrelation

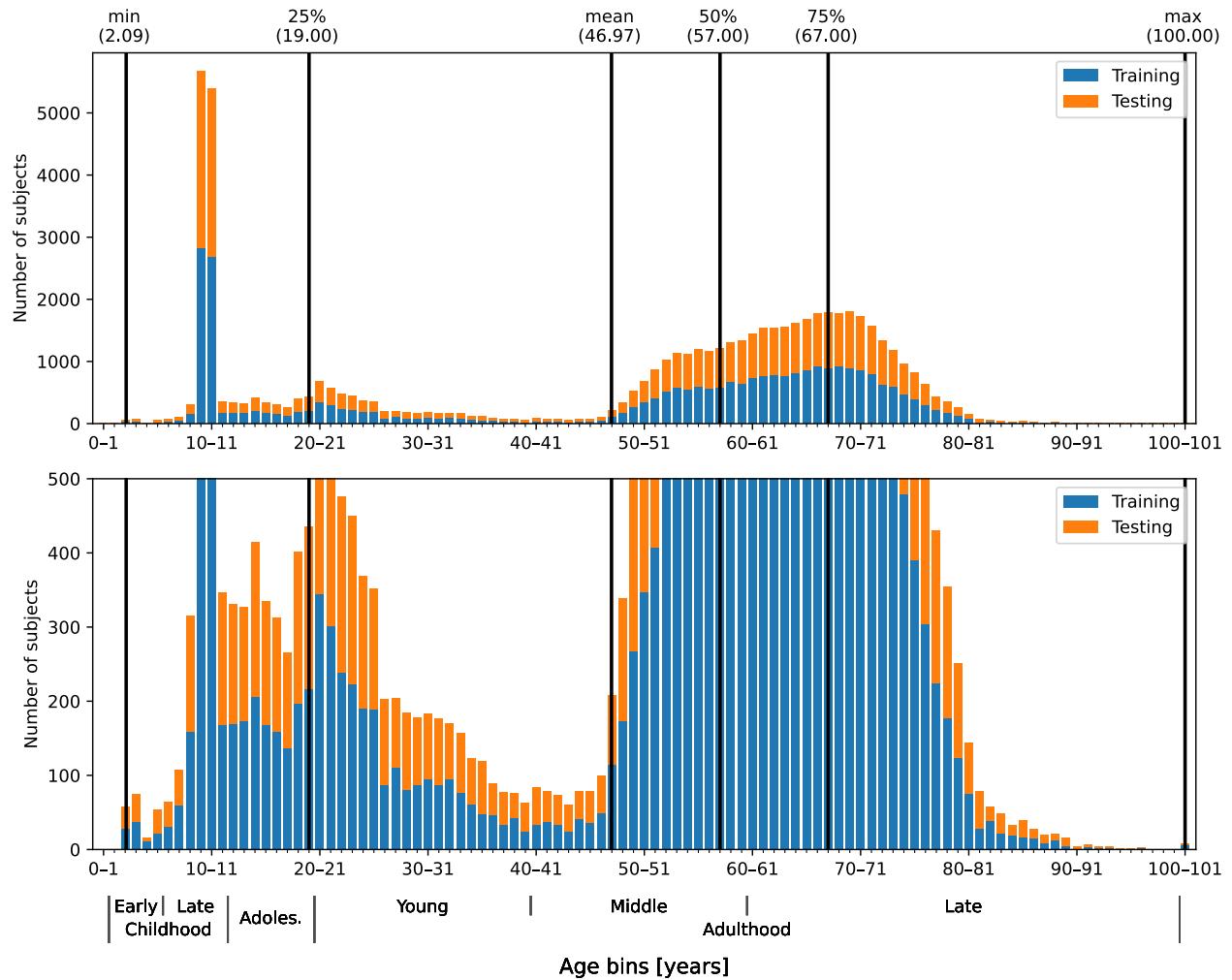


**Fig. S2: Dimensionality reduction of multimodal atlases**

**(A)** Spearman correlation matrix of original multimodal atlases. **(B) & (C): Left:** Cumulative explained variance (red) and eigenvalues (blue) of unrotated factors in a minimum residual factor analysis on the nuclear imaging atlases **(B)** and mRNA expression atlases **(C)**. The red vertical line marks the threshold of factors explaining at least 1% of variance. **Right:** Null distribution of total variance explained scores, if factor analyses estimated on permuted brain maps ( $n = 10,000$ ) are used to explain variance in the original data. Red lines indicate the observed explained variance. **(D) & (E):** Factors extracted from the nuclear

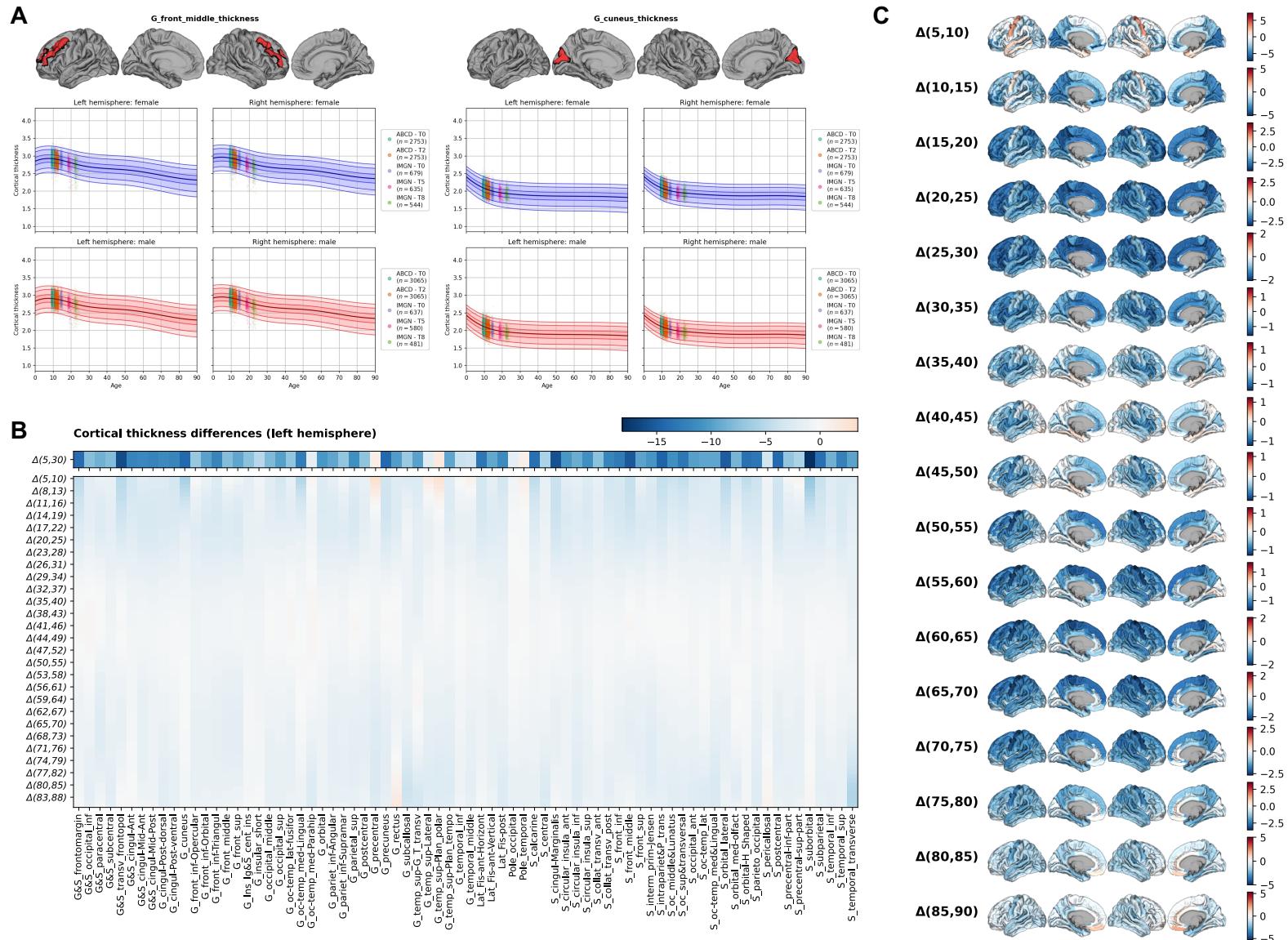
imaging (**D**) and mRNA expression (**E**) datasets after promax rotation. The **heatmaps** show Pearson correlations between the original atlases before factor analysis. **Stacked bar plots** show factor loadings for each original atlas on each factor. Factor names were derived from assigning each original atlas to the factor it loaded on most so that each original atlas appears exactly once in the overall factor names. (**F**) Spearman correlation matrix of the 20 derived factors and the microstructural atlas.

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**Fig. S3: Age distributions of the Braincharts cohort**

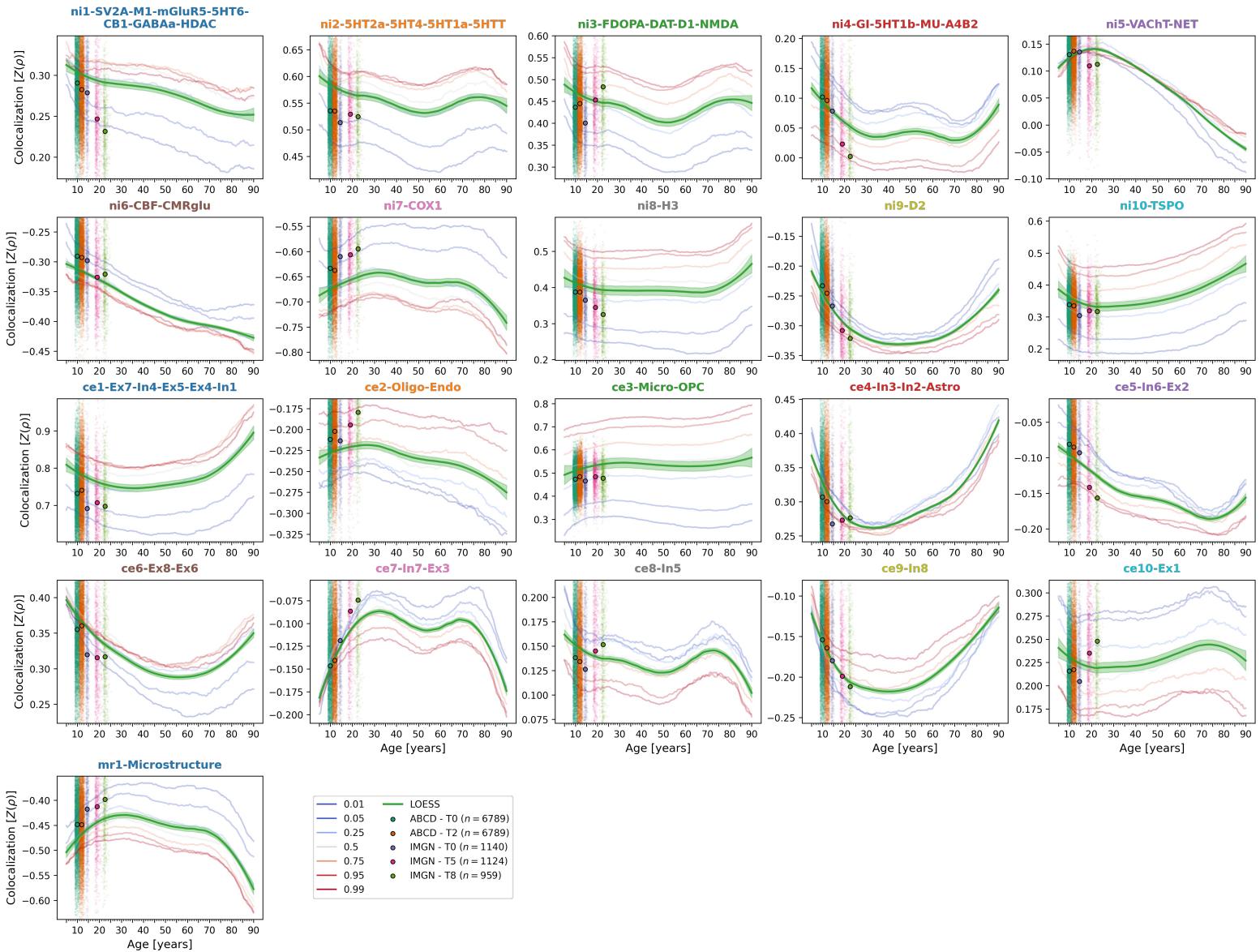
Age distribution in Braincharts model, displayed as **stacked histograms** (blue: training data, orange: testing data) with 1-year bins (bin “0–1”:  $\geq 0$  to  $< 1$  years, bin “1–2”:  $\geq 1$  to  $< 2$  years, ...). The lower panel is a copy of the upper panel with scaled y axis to visualize smaller bins. **Black vertical lines** show descriptive statistics for the whole dataset. The sharp peak at 9 to 11 years is caused by the ABCD study dataset, the smoother peak at 50 to 75 years is related to the UK Biobank study.



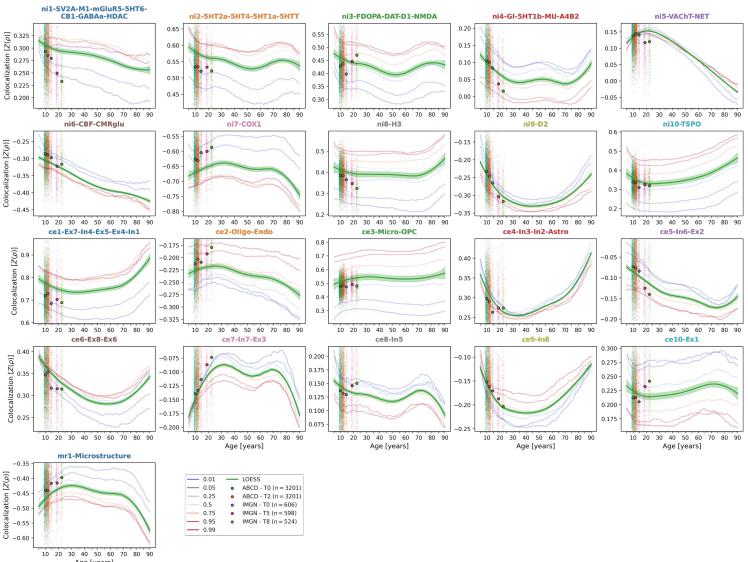
**Fig. S4: Lifespan cortical thickness development**

Cortical thickness data extracted from the reference model by Rutherford et al. (2022) and the IMAGEN cohort (Schumann et al., 2010). **(A)** Exemplary developmental trajectories of cortical thickness of two single bilateral brain regions for females (blue) and males (red). The darkest line represents the median, the brighter lines show the .01<sup>th</sup>, .05<sup>th</sup>, .25<sup>th</sup> as well as the .75<sup>th</sup>, .95<sup>th</sup>, and .99<sup>th</sup> centiles. **Scatters** show ABCD and IMAGEN subjects after adaptation to the Braincharts model at each study time points. See Animation S1 for all brain regions. **(B)** Left-hemispheric region-wise relative cortical thickness differences in percent-change from 5 to 30 years (upper row) and from 5 to 90 years, estimated using a sliding window with 1-year steps and 5-year window length (lower subfigure). **(C)** Cortical thickness development in 5-year steps, plotted are region-wise percent-change values.

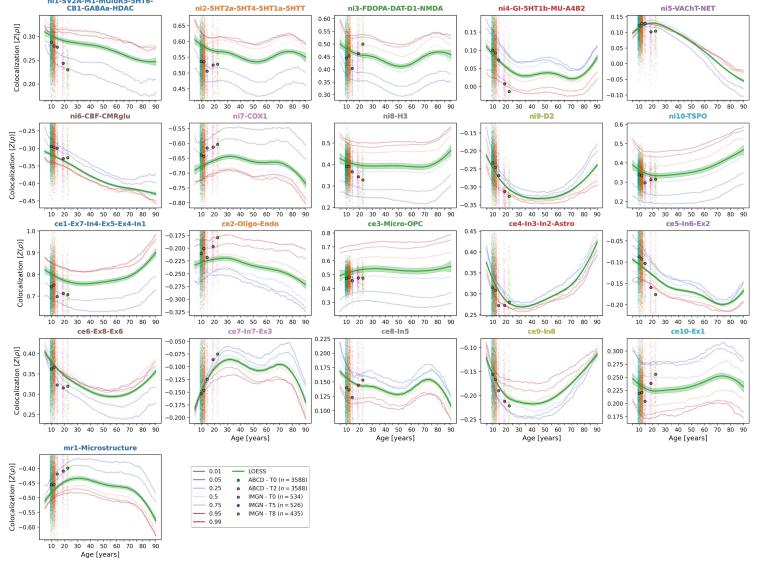
## A: Female-Male average



## B: Female only



## C: Male only

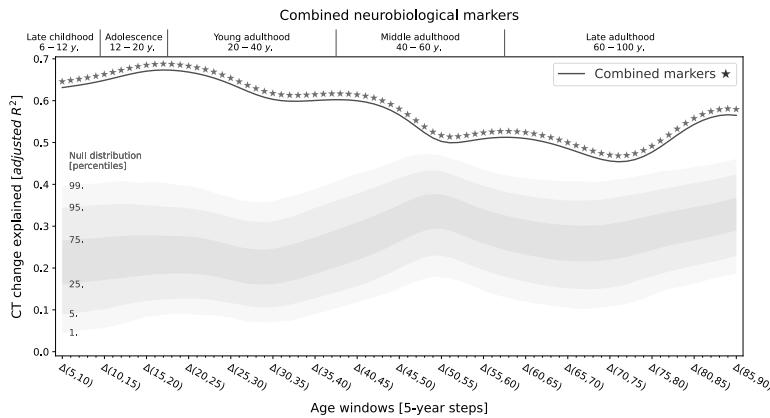


**Fig. S5: Spatial colocalization between cross-sectional CT and multilevel neurobiological markers: Validation cohort data and sex differences**

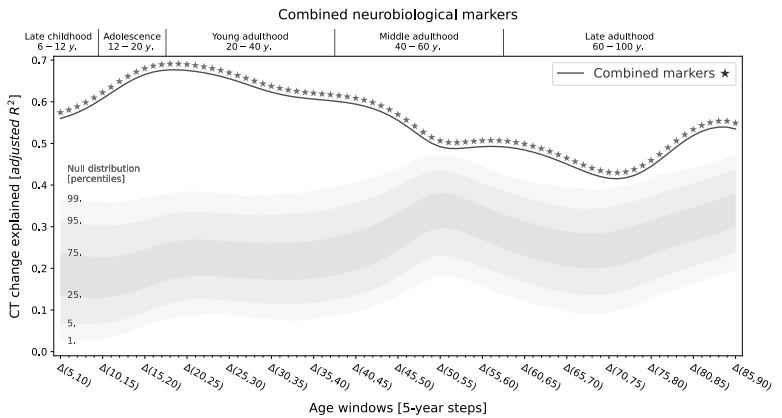
Lifespan trajectories of colocalization between multilevel neurobiological markers and cross-sectional CT. **(A)** Equivalent to Ext. Data Fig. 3 but with added individual subjects from ABCD and IMAGEN cohorts at each timepoint (**colored scatters**) with mean colocalization strength indicated by the **larger dots**. These serve to validate the observations based on modeled CT (i.e., strength and sign of the colocalizations). **(B)** and **(C)**: Results for modeled CT and ABCD/IMAGEN data, separately by sex. **Abbreviations:** CT = cortical thickness, MRI = magnetic resonance imaging, LOESS = locally estimated scatterplot smoothing.

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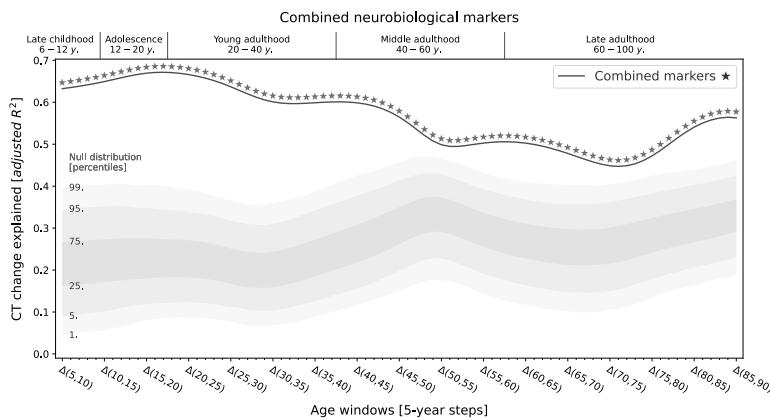
### A: Female-Male, 5-year window, 50<sup>th</sup> percentile (main)



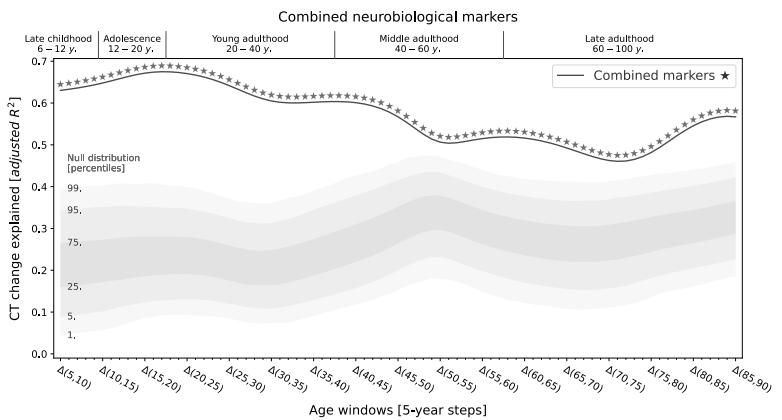
### B: Female-Male, 5-year window, 50<sup>th</sup> percentile (baseline)



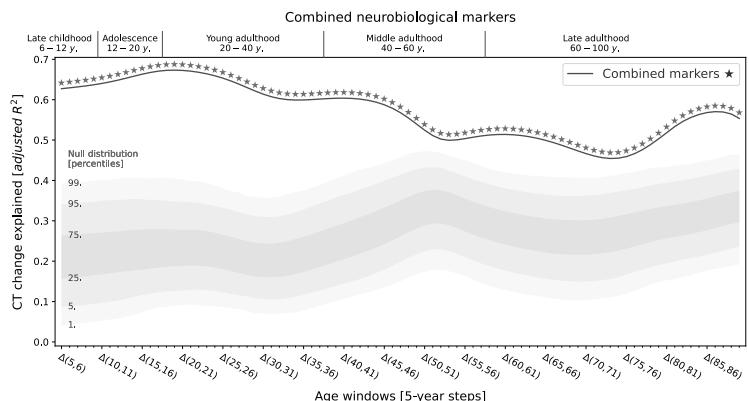
### C: Female, 5-year window, 50<sup>th</sup> percentile



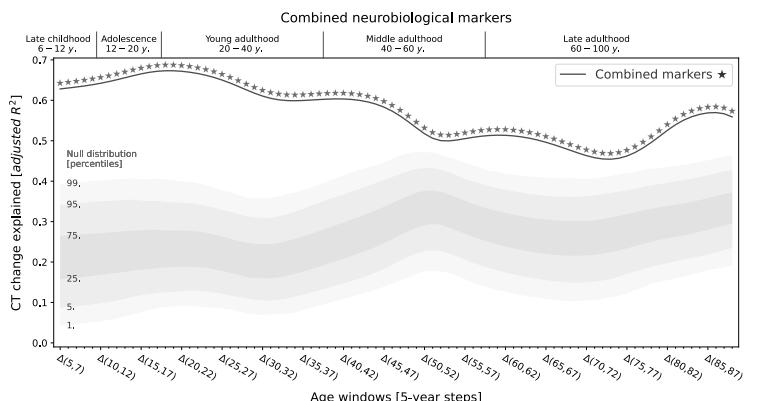
### Male, 5-year window, 50<sup>th</sup> percentile



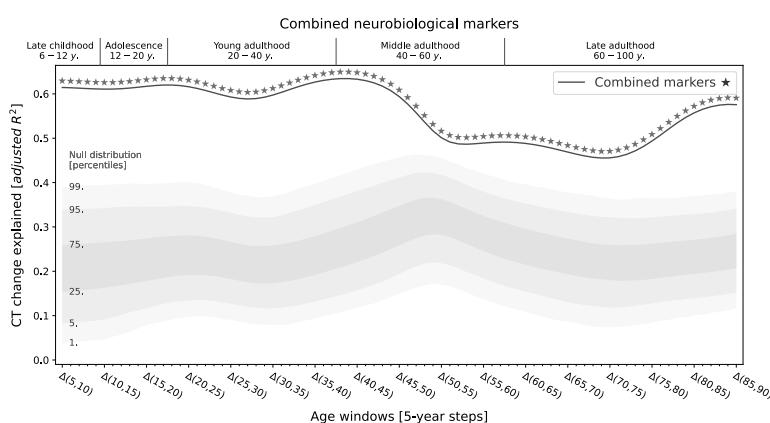
### D: Female-Male, 1-year window, 50<sup>th</sup> percentile



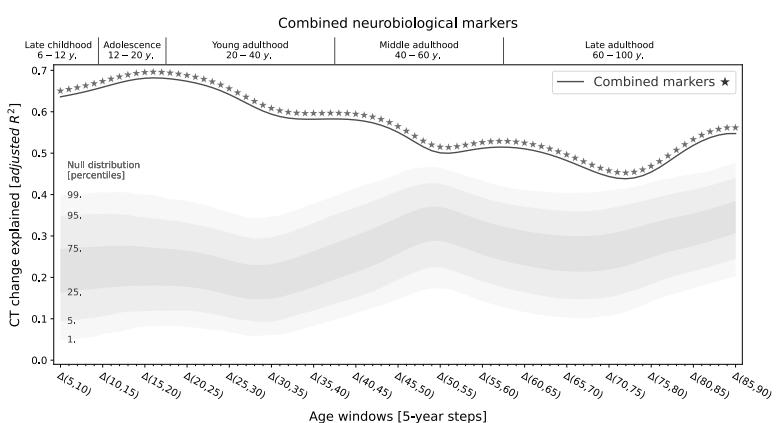
### Female-Male, 2-year window, 50<sup>th</sup> percentile



### E: Female-Male, 5-year window, 1<sup>th</sup> percentile



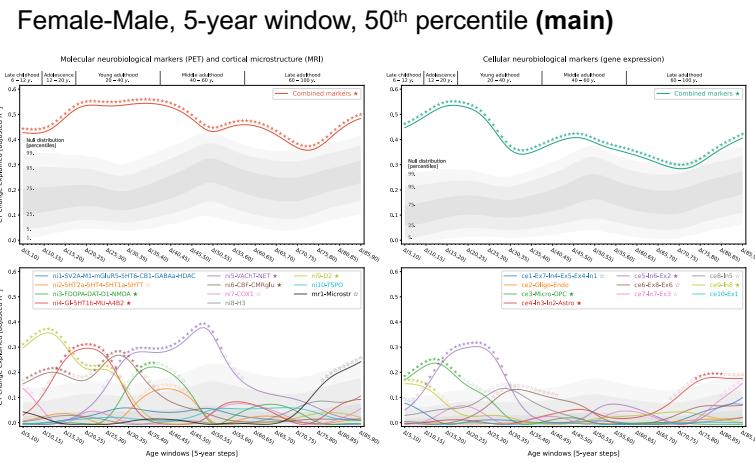
### Female-Male, 5-year window, 99<sup>th</sup> percentile



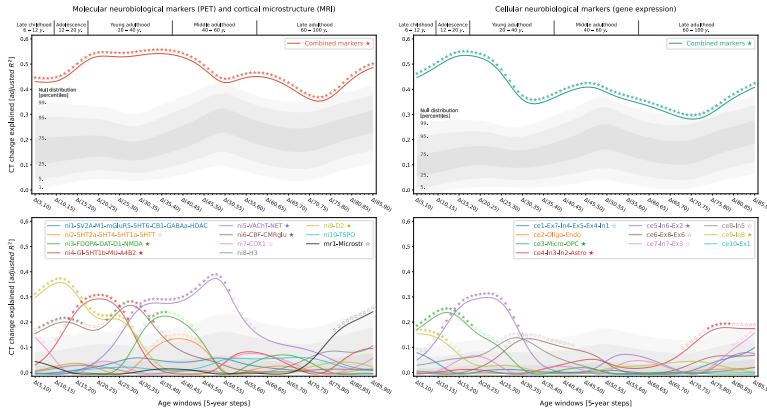
**Fig. S6: Joint multivariate regression result in different analysis cases**

**(A)** Multivariate regression on cortical thickness change across the lifespan using all predictors, neuroimaging and mRNA expression combined, settings as in main analyses. **(B)** Results after correcting the change data for baseline CT. **(C)** Results for only male or only female CT reference data. **(D)** Results with sliding window length of 1 or 2 years instead of 5 years. **(E)** Results for first or 99<sup>th</sup> instead of 50<sup>th</sup> percentile CT reference data. Please refer to main Fig. 2 for descriptions of the panel elements.

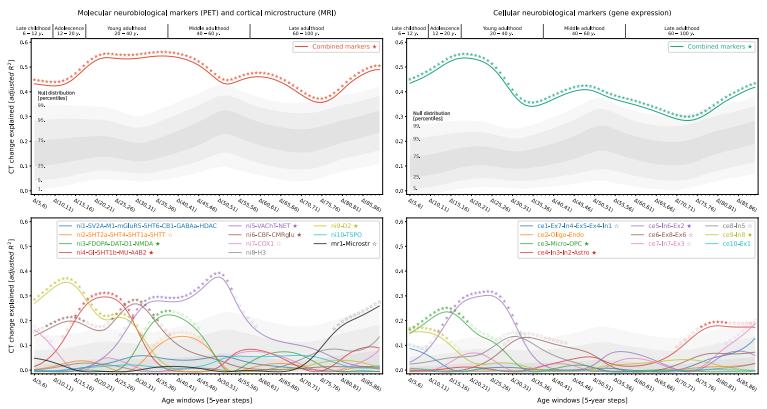
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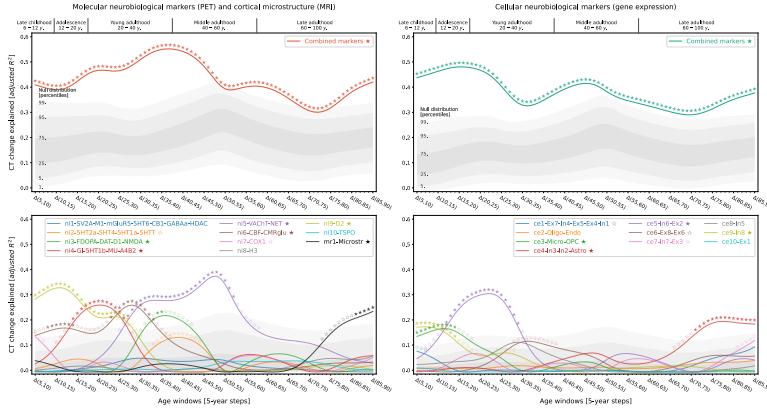
### **Female, 5-year window, 50<sup>th</sup> percentile**



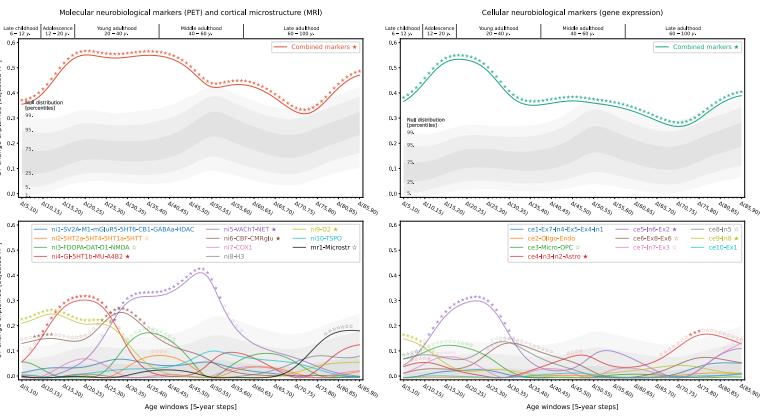
### Female-Male, **1-year window**, 50<sup>th</sup> percentile



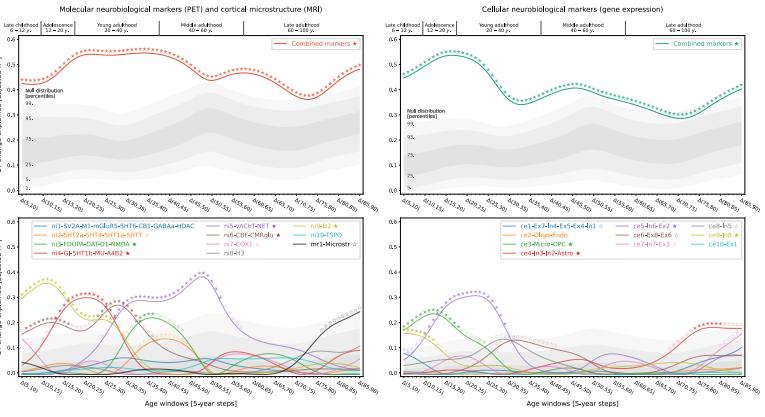
### Female-Male, 5-year window, 1<sup>th</sup> percentile



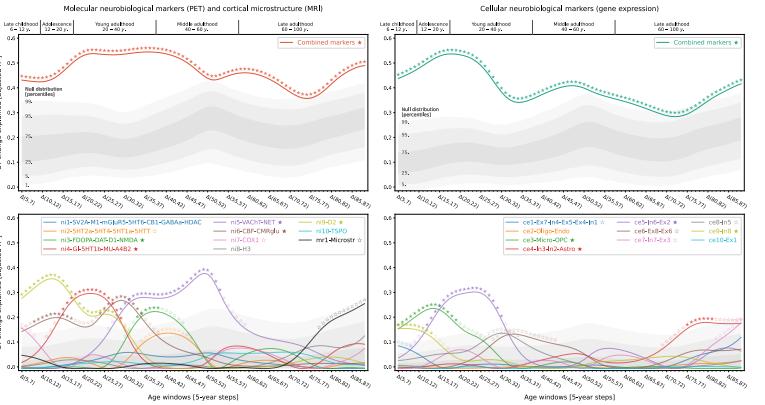
### Female-Male, 5-year window, 50<sup>th</sup> percentile (**baseline**)



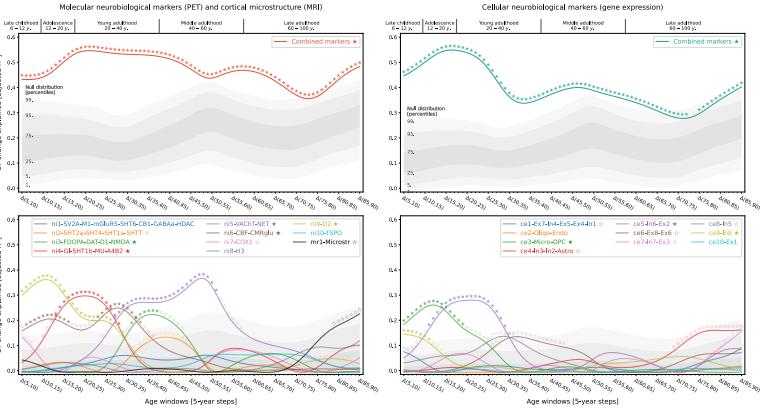
### **Male, 5-year window, 50<sup>th</sup> percentile**



### Female-Male, **2-year window**, 50<sup>th</sup> percentile



### Female-Male, 5-year window, **99<sup>th</sup> percentile**

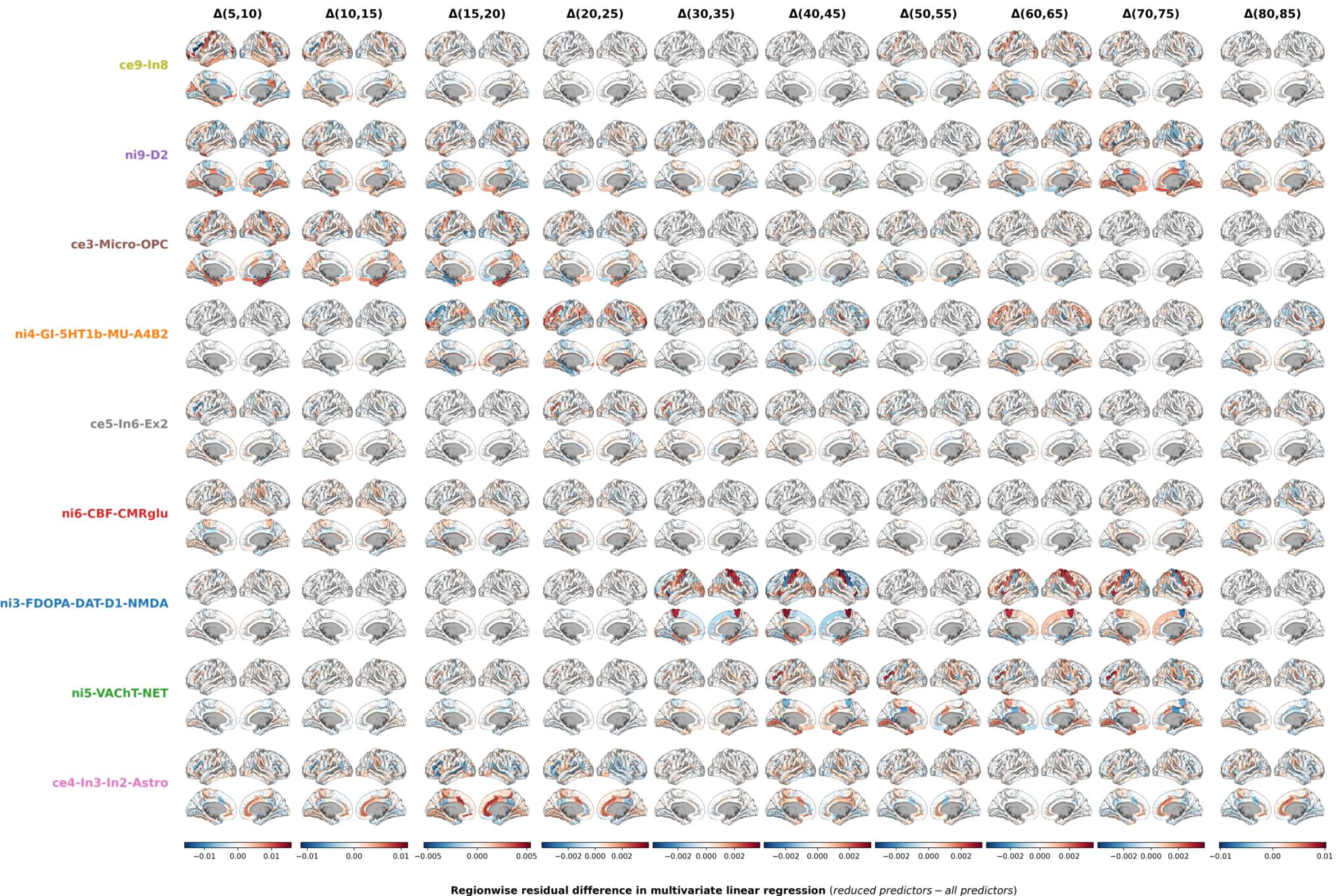


**Fig. S7: Influence of sex, sliding window length, and cortical thickness reference percentile on main regression results**

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Univariate and multivariate regression results for the cases outlined in Fig. S6. Please refer to main Fig. 2 for descriptions of the panel elements.

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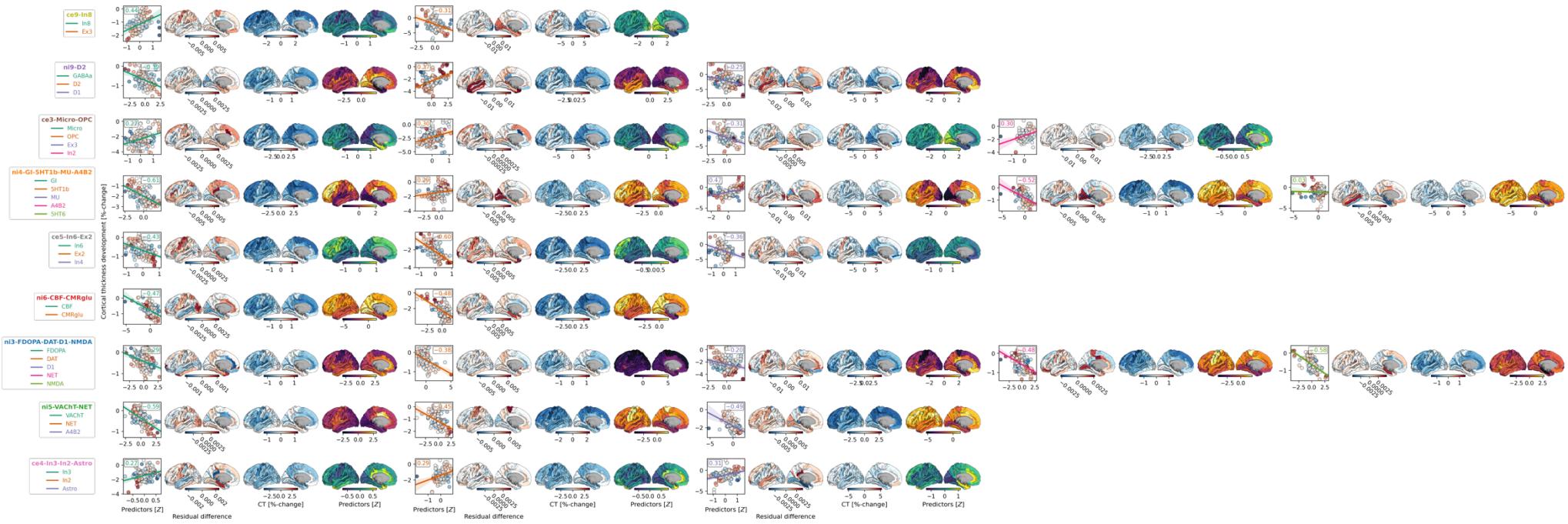


**Fig. S8: Contribution of individual brain regions to explained lifespan cortical thickness change**

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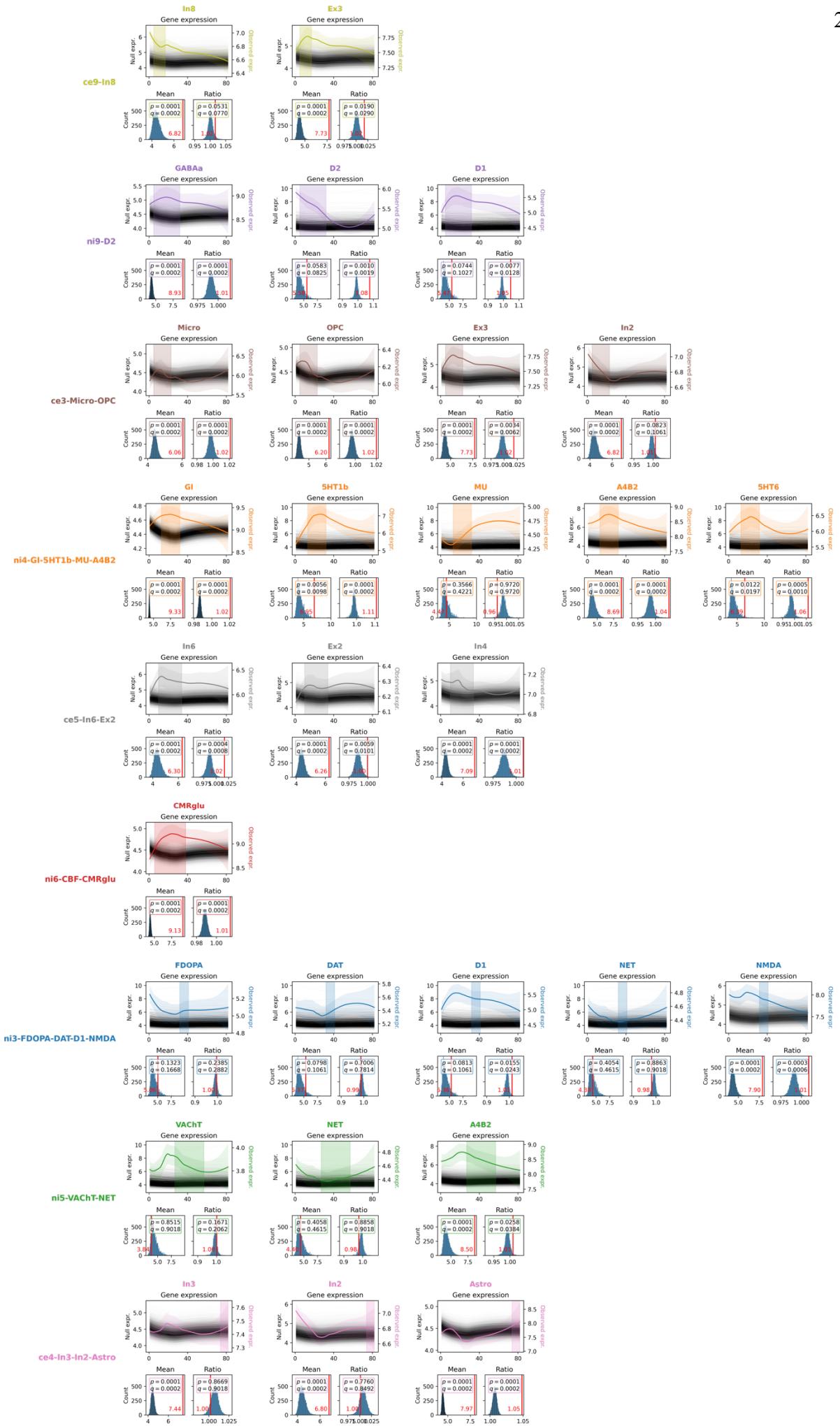
Parcelated brain plots show residual differences as estimated in the main dominance analyses. Residual differences were calculated for each predictor  $x$  as the difference between prediction errors resulting from a multivariate linear regression with all 7 predictors included and the prediction errors under exclusion of  $x$ .

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**Fig. S9: Cortical distributions of residual differences, cortical thickness changes, and average values of the original atlases associated to each selected predictor**

This figure corresponds to each row of Ext. Data Fig. 4 and mirrors the layout of Fig. 3B. Please see these for descriptions of the panel elements.

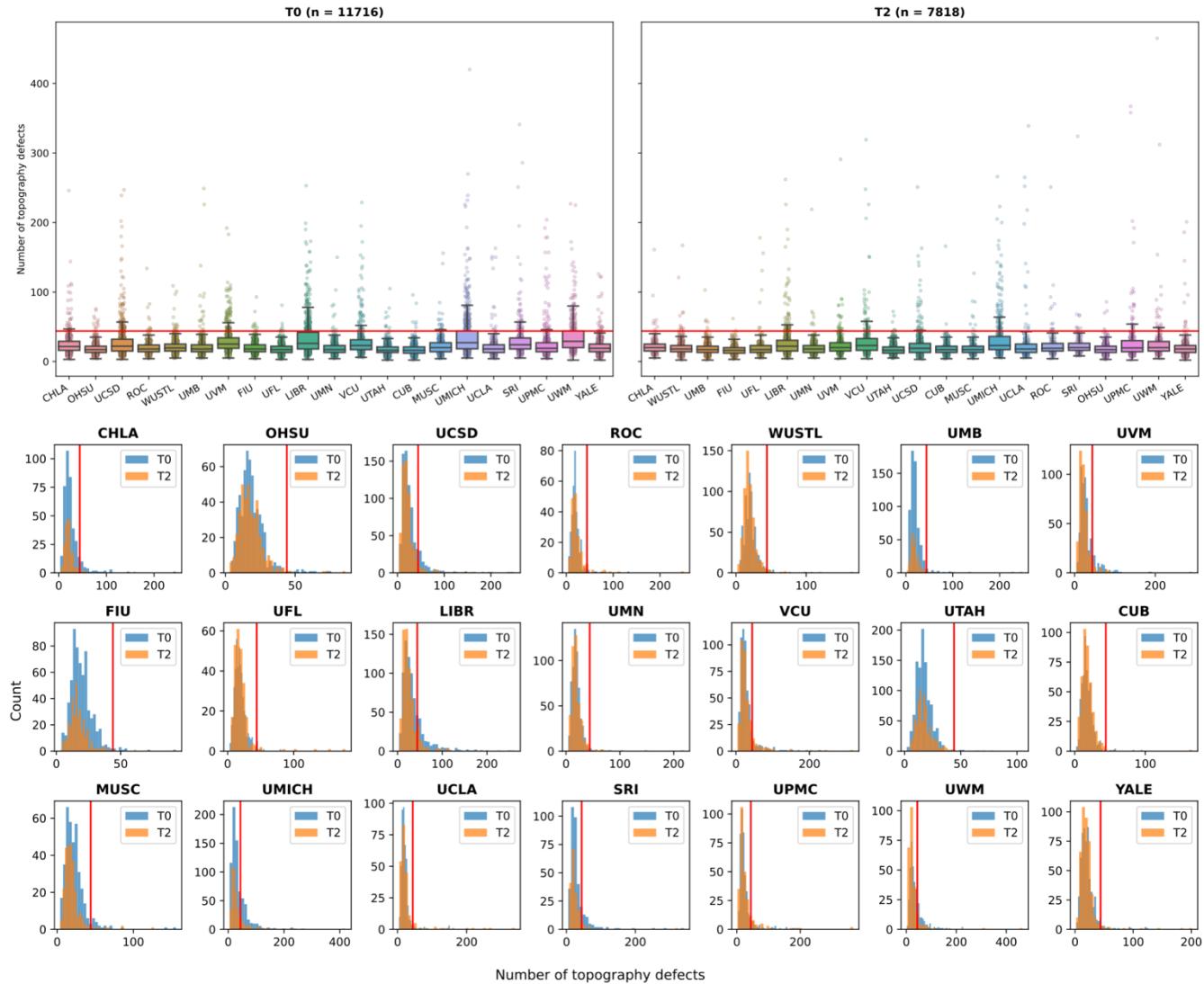


**Fig. S10: Null trajectories and test null distributions for developmental gene expression data**

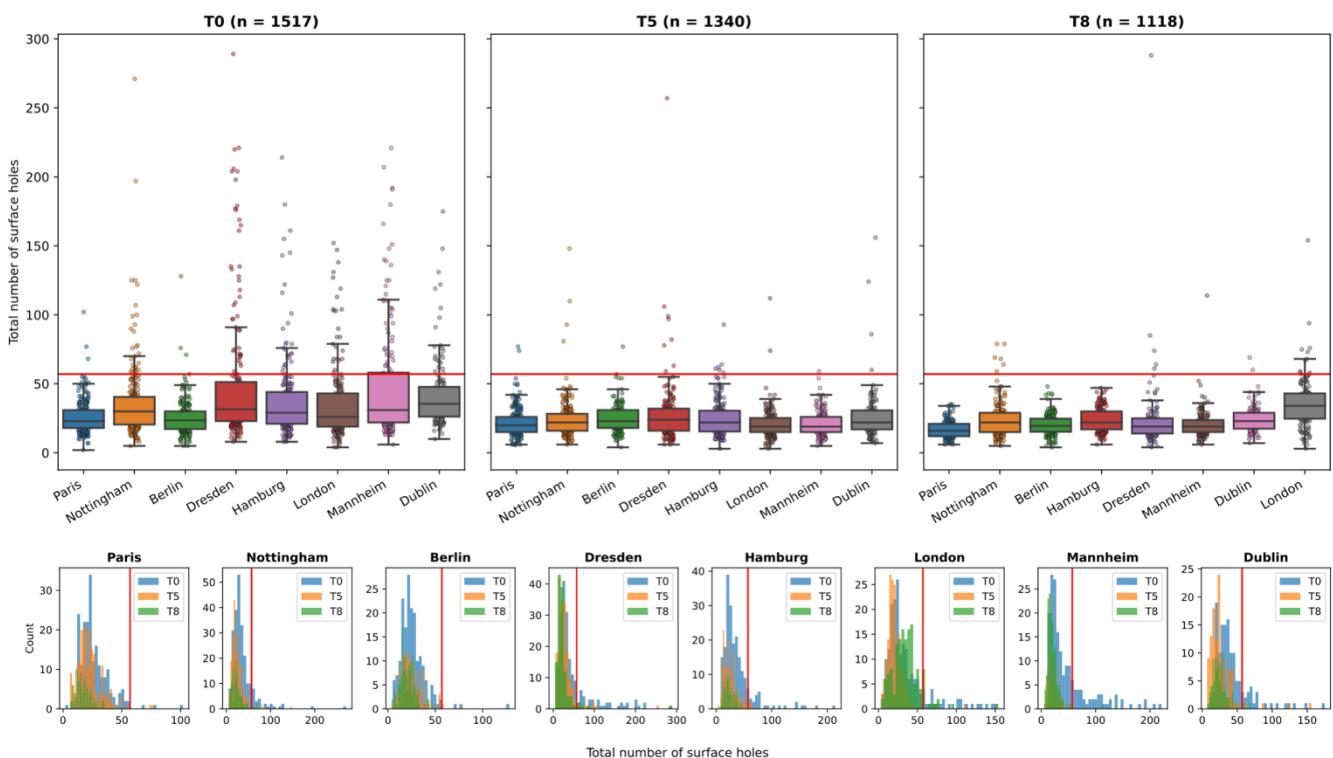
Detailed test results corresponding to main Fig. 4. For each multilevel neurobrain marker (**rows**) and each gene/ gene set associated to the original brain atlases (**columns per row**), we show the observed gene expression trajectory (**colored, left y axis**), and  $n = 10,000$  null trajectories (**grey, right y axis**). The histograms below show null distribution for the mean expression during the significant CT period (**left**) and the ratio of mean expression during vs. outside the significant CT period (**right**). The **red lines and numbers** indicate observed mean/ ratio values; p and q indicate nominal and FDR-corrected empirical p values.

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## A: ABCD



## B: IMAGEN

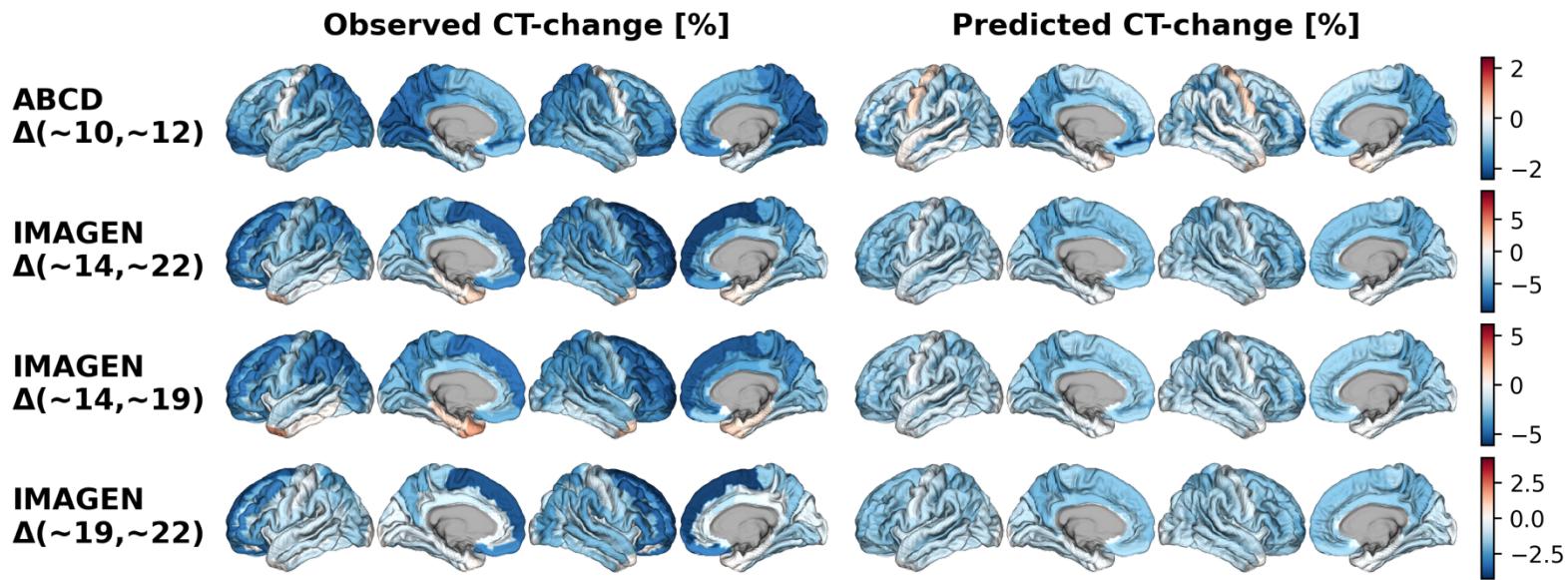


**Fig. S11: Euler number-based quality control of ABCD and IMAGEN data**

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Distributions of Euler number-related metrics in ABCD (**A**) and IMAGEN (**B**) datasets at different study time points. The upper and lower sub-panels of A and B visualize the distributions of the quality control metrics in different ways. For IMAGEN, the sum of the two hemispheric Euler numbers, and for ABCD, the variable “apqc\_smri\_topo\_n defect” was used. Subjects were excluded if they exceeded a threshold of  $Q3 + 1.5 * IQR$  calculated across study time points within each study.

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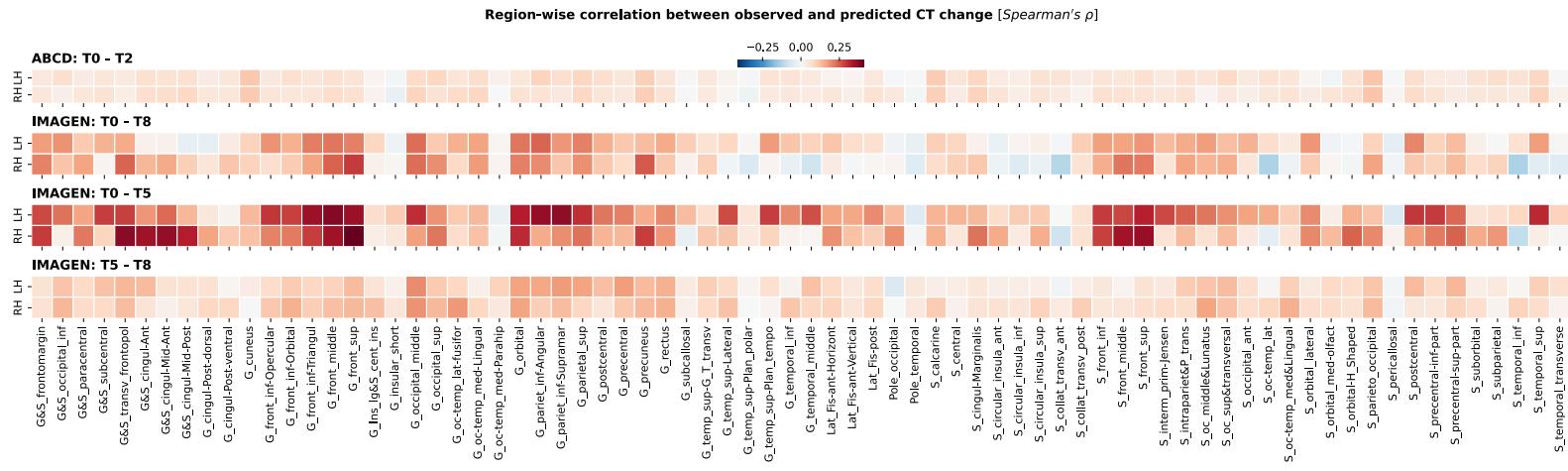


**Fig. S12: Observed and predicted ABCD and IMAGEN cohort-average cortical thickness change**

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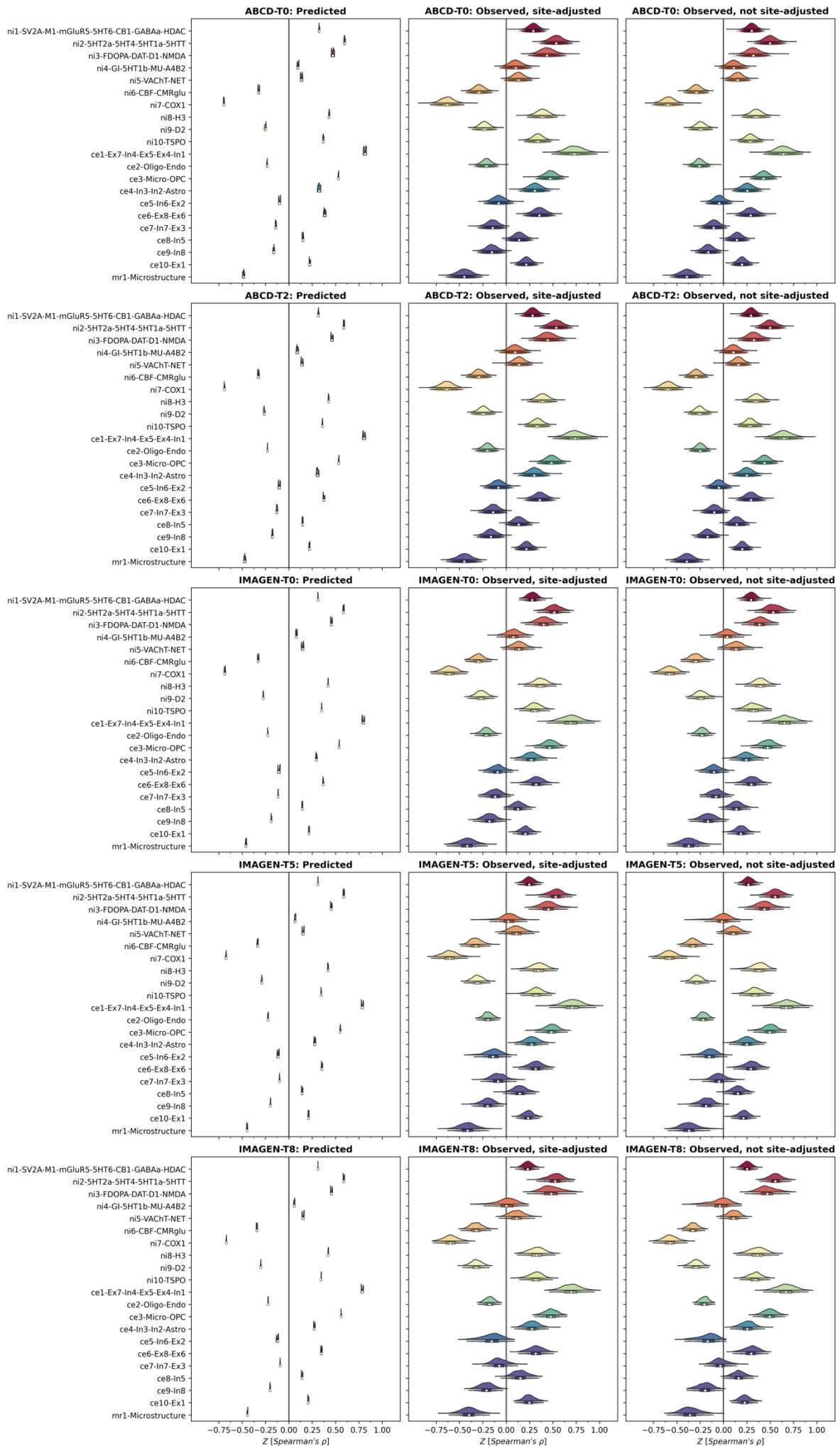
Average relative CT change in percent across four time periods in the ABCD and IMAGEN datasets as observed (**left**) and as predicted (**right**) by the Braincharts model based on age and sex of the subjects.

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**Fig. S13: Region-wise correlation between predicted and observed cortical thickness change**

Regional correlation (Spearman's rho) between relative CT changes as predicted by the Braincharts model (percent-change of predicted CT values from timepoint one to timepoint two) and relative CT change as observed in ABCD and IMAGEN datasets across each time period. Predicted CT change was calculated for each subject individually based on their age and sex.

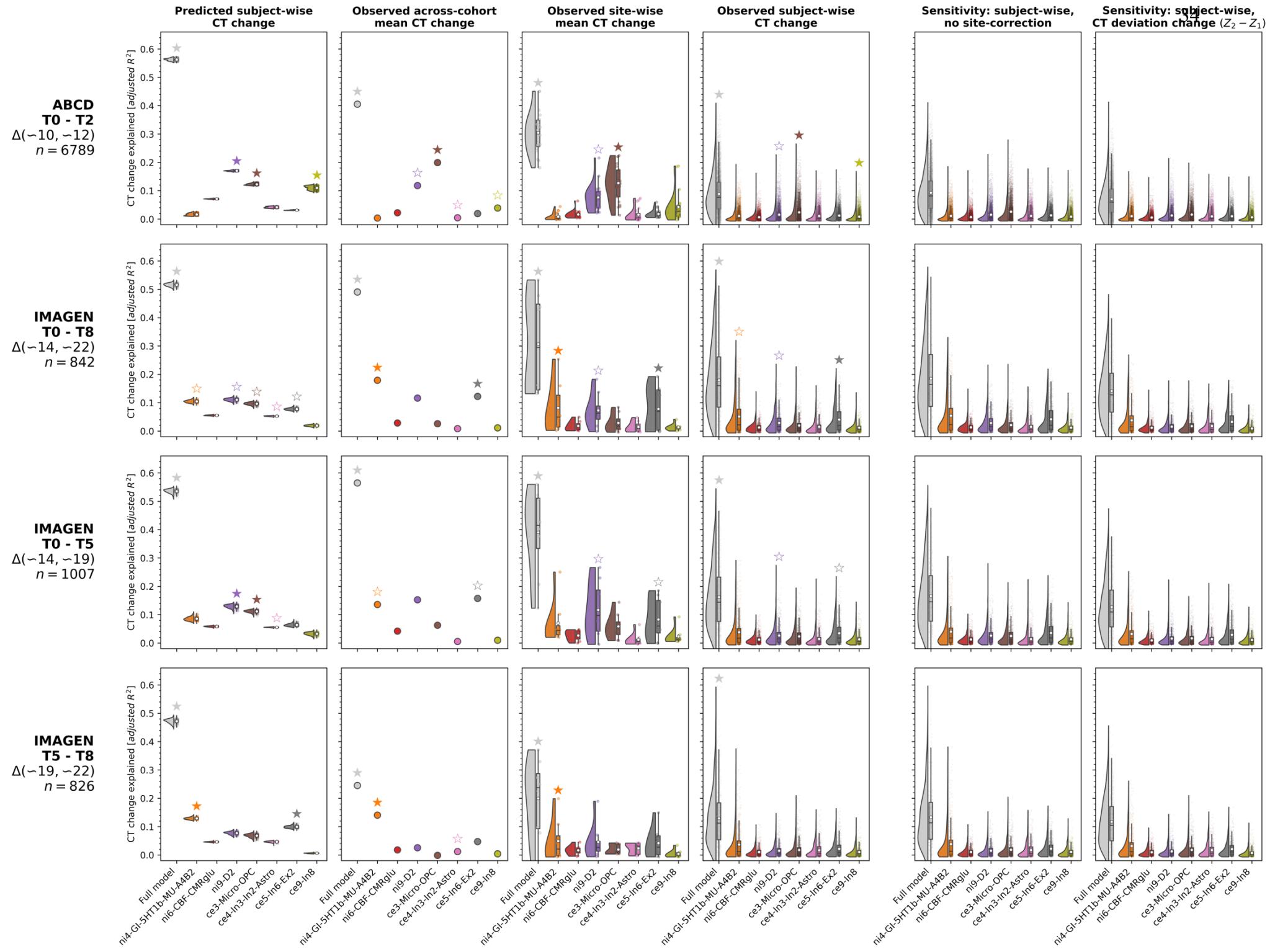


**Fig. S14: Spatial colocalization between cross-sectional ABCD and IMAGEN cortical thickness data and multimodal neurobiological markers**

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Spatial colocalization with multimodal predictors quantified as Z-transformed Spearman correlation for each ABCD and IMAGEN subject at each study time point (**rows**) based on CT data as predicted by the Braincharts model (**first column**), observed CT data after site-correction using the Braincharts model (**second column**), and original observed CT data without site-correction (**third column**). The latter serves the purpose to exclude potential overfitting effects due to the baseline ABCD data being used in estimation of the Braincharts model. See also the trajectory plots (Ext. Data Fig. 3 and Fig. S5).

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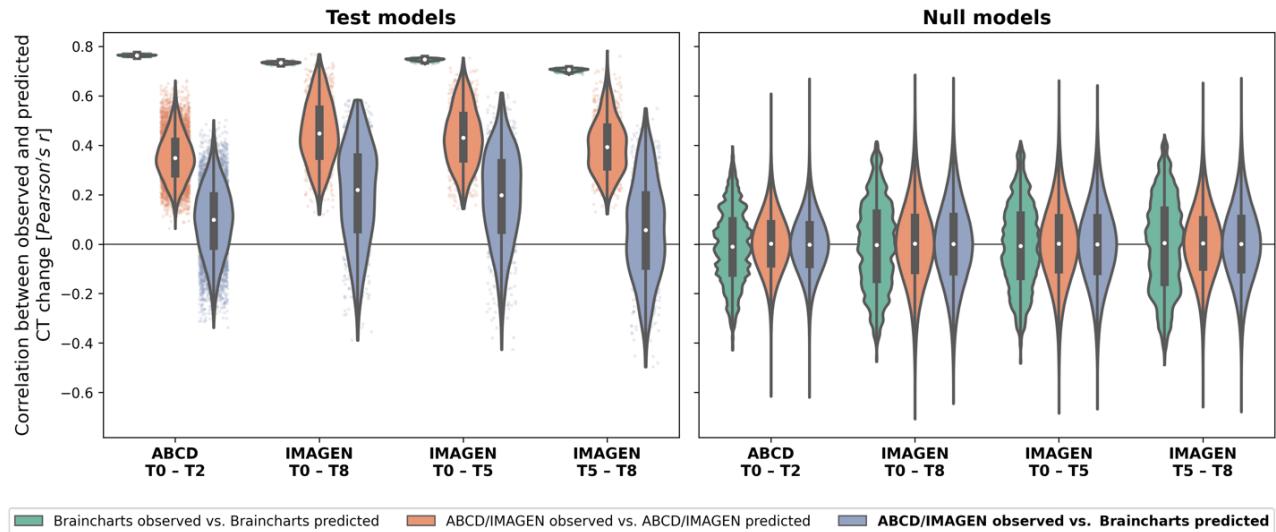


**Fig. S15: Detailed Spearman correlation results showing colocalization patterns between ABCD and IMAGEN CT change and multimodal predictors**

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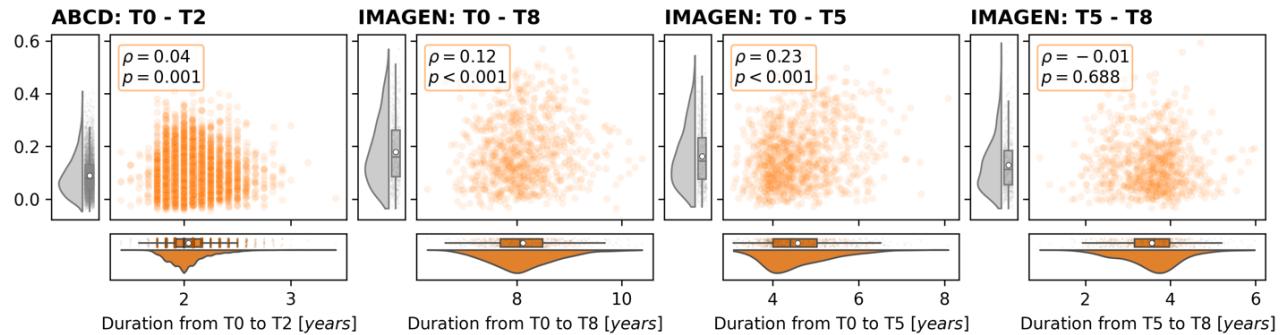
Add-on to Ext. Data Fig. 5. Instead of multivariate regression analyses, Spearman correlations were calculated, to capture the sign of the spatial associations. As of this demonstrational purpose, no significance tests were performed.

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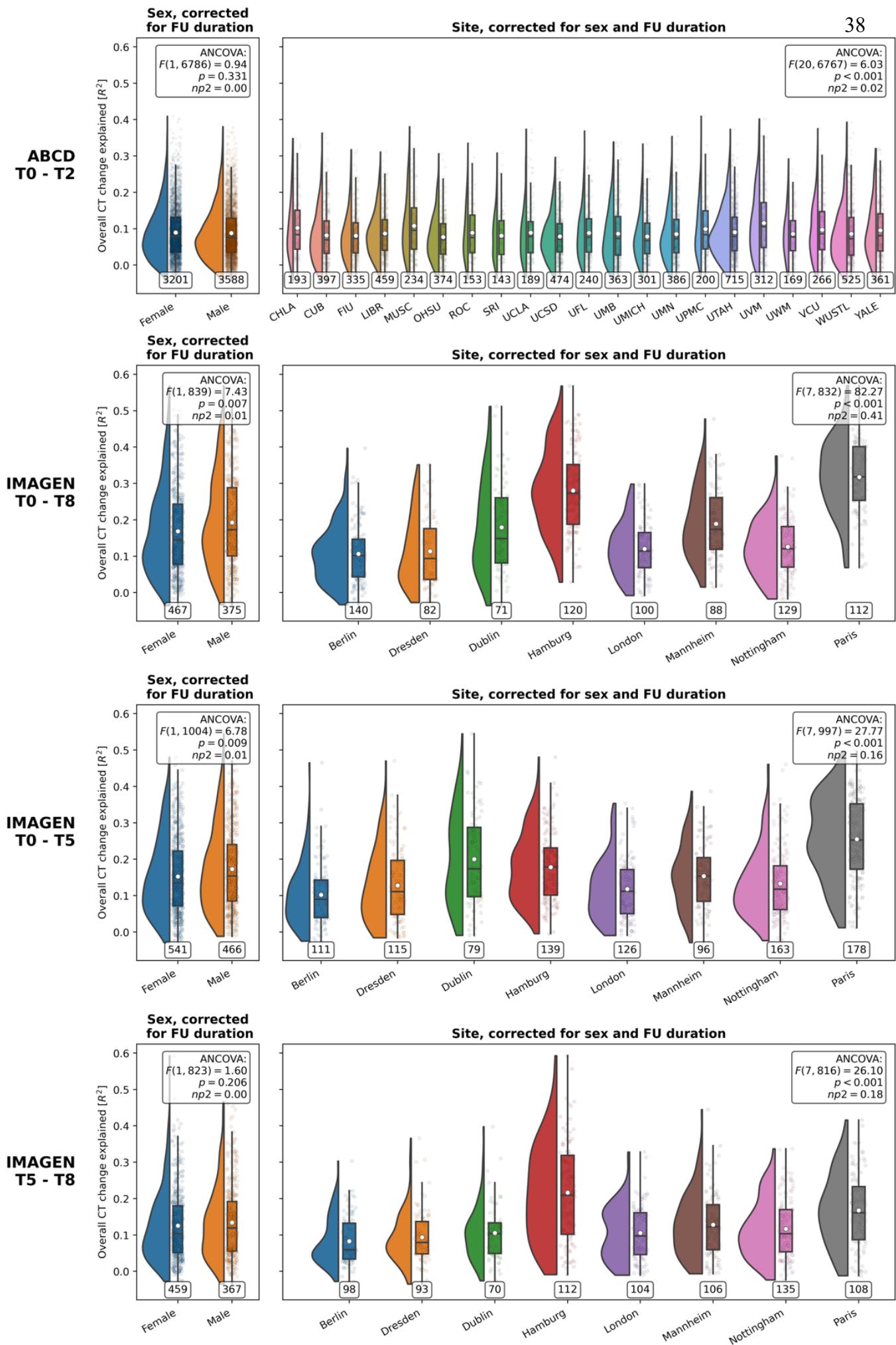
**Fig. S16: Generalization of CT change prediction models trained on normative single-subject data to observed data**

Evaluation of the generalizability of normative CT change prediction (= **blue violins**). The **y axis** shows regression model fit as the Pearson correlation between observed and predicted responses (i.e., CT change patterns). The **left panel** shows analyses based on the actual neurobiological marker brain maps, the **right panel** shows results based on permuted maps (1,000 iterations). **Green violins:** Fit of regression models estimated on each subject's *normative* CT change patterns as predicted by the "Braincharts" model. **Orange violins:** Fit of regression models estimated on each subject's observed CT change patterns. **Blue violins:** Fit of models estimated on the *normative* CT change patterns but applied to the *observed* CT change. The result indicates how well the normative model, as the "population average", performs in representing each subject's CT associations to multilevel neurobiological markers.



**Fig. S17: Effects of follow-up duration on total explained cortical thickness change**

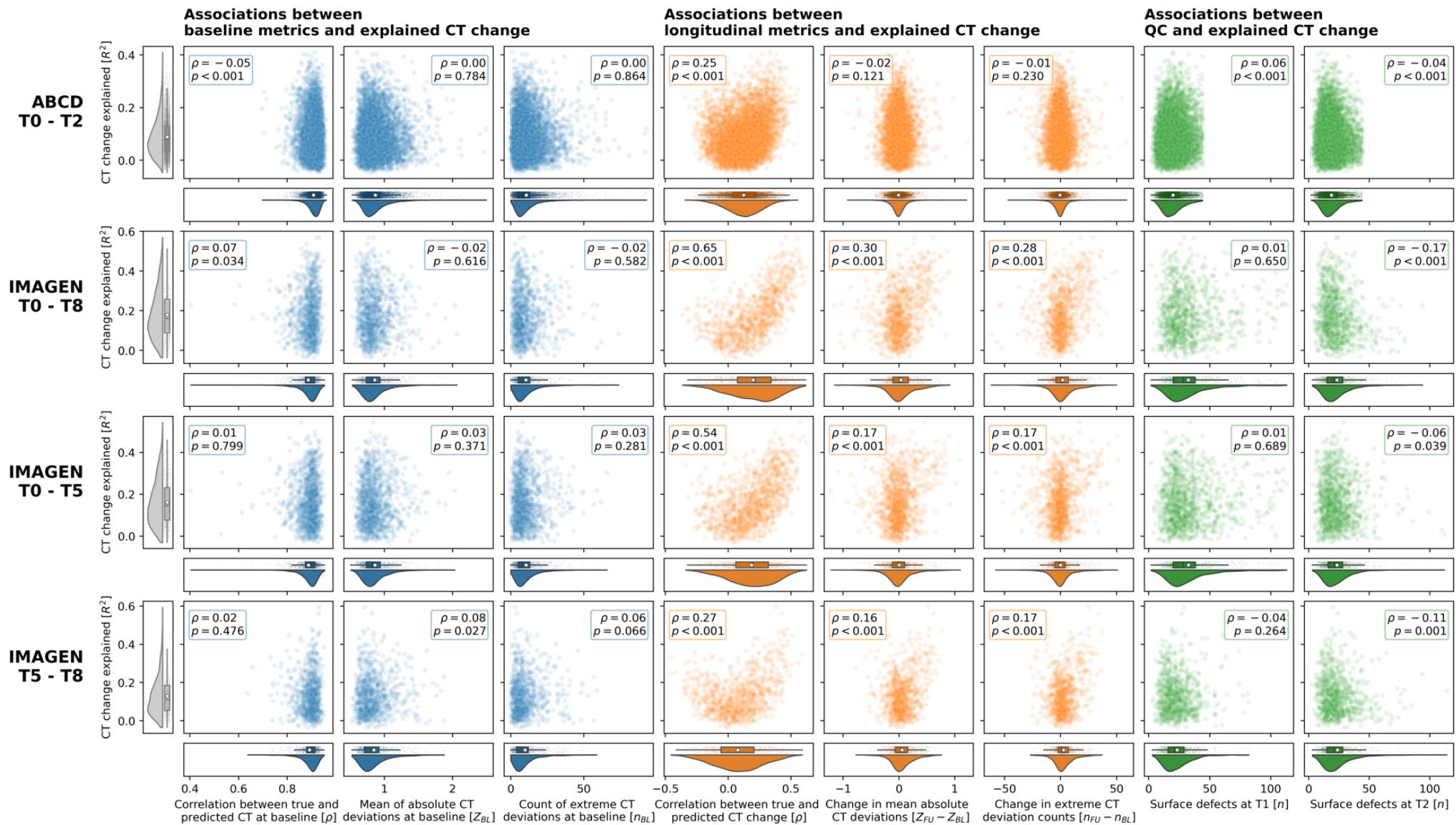
Correlations between follow-up duration for each dataset and at each time period (**x axes**) with total explained CT change variance (**y axes**). **Boxes** in the upper corners of each panel contain Spearman's rho and the associated parametric *p* value for each bivariate association.



**Fig. S18: Effects of sex and site on total explained cortical thickness change variance**

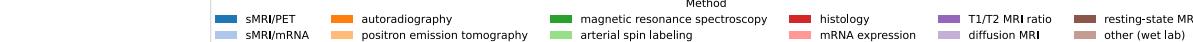
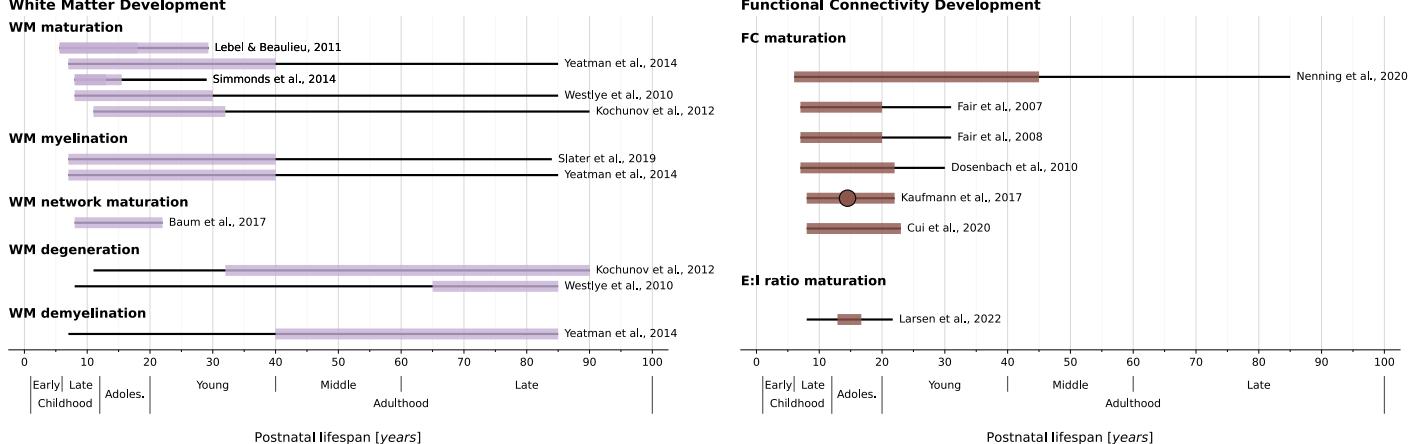
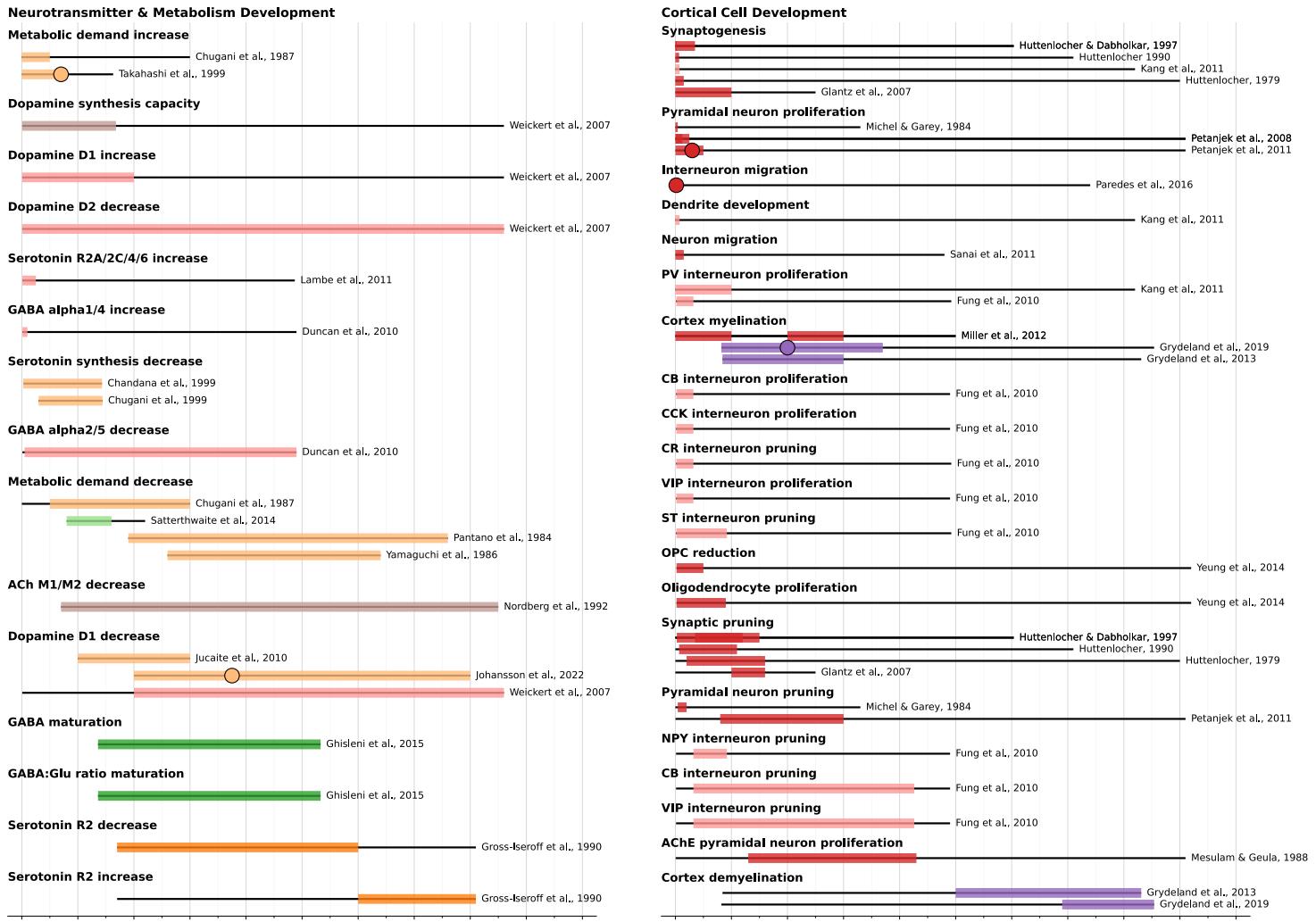
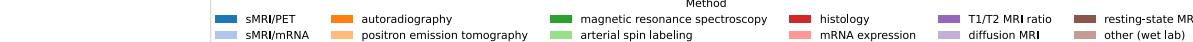
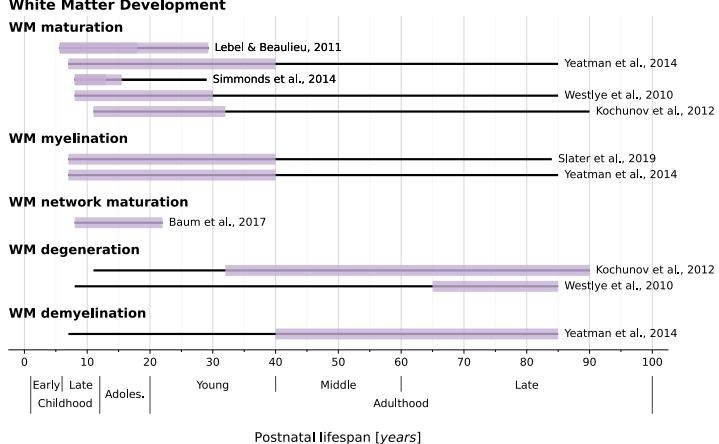
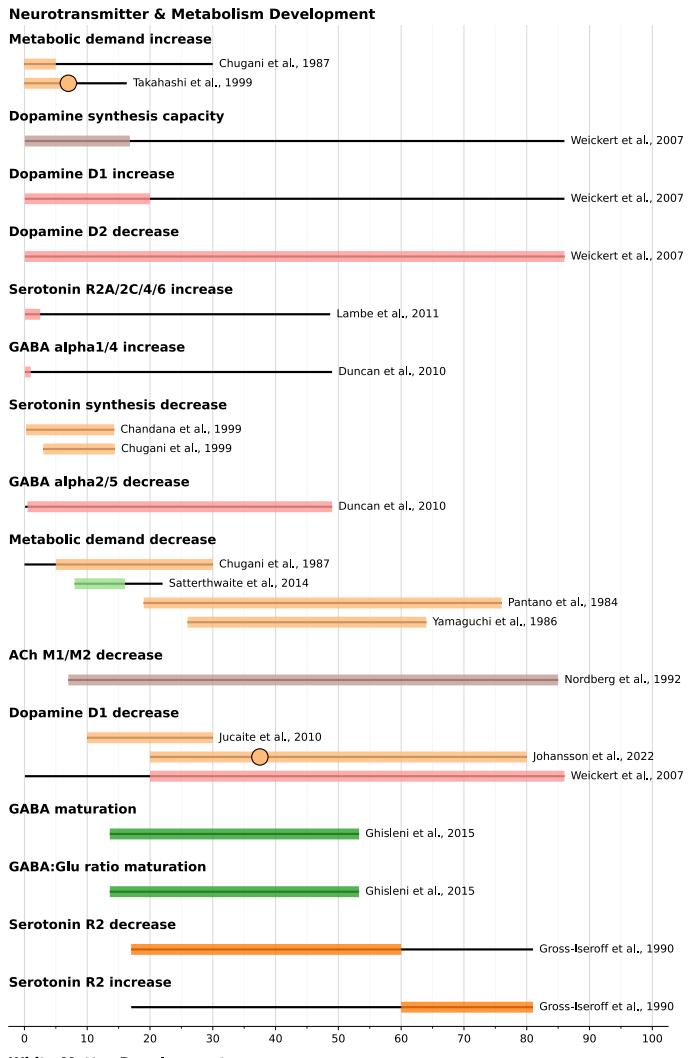
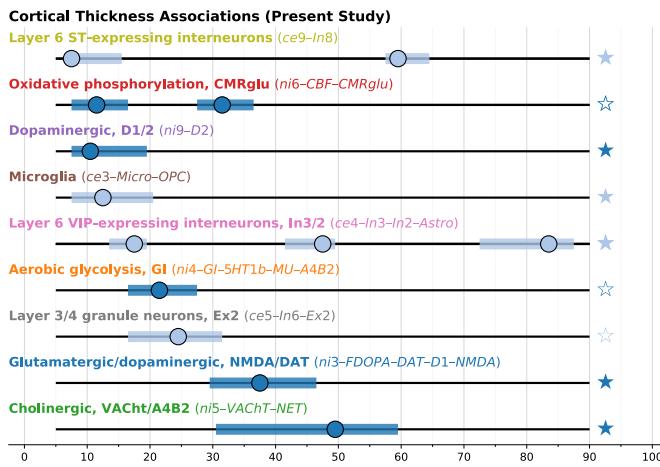
Comparisons testing if the overall extent to which ABCD and IMAGEN CT change was explained (y axes) across each tested time period (**rows**) varied by binary sex (**column 1**) and site (**column 2**). Raincloud plot elements as described above. Sex was compared using T tests with Welch's correction, effect sizes are expressed as Hedge's g. Sites were compared using analyses of covariance (ANCOVAs) assessing the effect of site on explained CT change variance, including binary sex as covariate. Effect sizes are expressed as eta-squared (np2).

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**Fig. S19: Effects of predictive performance, subject-level atypical development, and surface reconstruction quality on explained cortical thickness**

Scatterplots show relationships between cohort- and time period-wise (**rows**) total explained CT change (**y axes**) as estimated in subject-wise dominance analyses. **X axes:** **Columns 1 and 4:** Model fit; correlation between observed and predicted baseline CT or CT change. **Columns 2 and 5:** CT deviations; absolute CT deviation Z scores or their longitudinal change. **Columns 3 and 6:** CT deviations; counts of extreme deviations per subject or their longitudinal change (defined as deviation  $Z > 2$ ). **Columns 7 and 8:** Data quality: Total Euler number, FreeSurfer's quality control metric for surface reconstruction. **Blue plots** indicate baseline metrics, **orange plots** indicate longitudinal metrics, **green plots** indicate associations with the Euler number at the first and second timepoint of each studied time period. **Boxes** in the upper corners of each panel contain Spearman's rho and the associated parametric  $p$  value for each bivariate association.



**Fig. S20: Summary of previous literature on processes involved in human brain development and maturation**

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Visualization of published results on correlates of human CT development and maturation. This collection is not exhaustive. The selection is limited to *in vivo* and postmortem studies in humans. The **upper two panels** are replicated from main Fig. 6 and are shown for completeness. **Thin black lines** depict the age range covered by each study. **Thick colored bars** show the time period in which an association between cortex measures and the respective study target was reported. If available, peaks of these associations are marked by **circles**. Results are **grouped** by the broad area of research, **colors** code the applied methodology. All references can be found in the supplementary reference list (Chandana et al., 2005; D. C. Chugani et al., 1999; H. T. Chugani et al., 1987; Cui et al., 2020; Dosenbach et al., 2010; Duncan et al., 2010; Fair et al., 2007, 2008; Fung et al., 2010; Ghisleni et al., 2015; Glantz et al., 2007; Gross-Isseroff et al., 1990; Grydeland et al., 2013, 2019; Huttenlocher, 1979, 1990; Huttenlocher & Dabholkar, 1997; Johansson et al., 2022; Jucaite et al., 2010; Kang et al., 2011, 2011; Kaufmann et al., 2017; Kochunov et al., 2012; Lambe et al., 2011; Larsen et al., 2022; Lebel & Beaulieu, 2011; Mesulam & Geula, 1988; Michel & Garey, 1984, 1984; Miller et al., 2012; Nenning et al., 2020; Nordberg et al., 1992; Pantano et al., 1984; Paredes et al., 2016; Parker et al., 2020; Patel et al., 2019; Petanjek et al., 2008, 2011; Sanai et al., 2011; Satterthwaite et al., 2014; Shin et al., 2018; Simmonds et al., 2014; Slater et al., 2019; Takahashi et al., 1999; Vidal-Pineiro et al., 2020; Weickert et al., 2007; Westlye et al., 2010; Wong et al., 2018; Yamaguchi et al., 1986; Yeatman et al., 2014; Yeung et al., 2014).

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