Large-scale analysis of structural brain asymmetries in schizophrenia via the ENIGMA consortium

Supplementary information

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Supplementary note 1: Overview of statistical models for regression and partial correlation analyses

Below is an overview of the models for the linear regression and partial correlation analyses that were run by each participating site, and from which summary statistics for meta-analysis by the central analysis group were extracted. Model numbers refer to those indicated in the main manuscript text. The independent variable highlighted in **bold** is the predictor of interest in each model, for which effects were combined across datasets in random-effects meta-analysis.

Abbreviations used in models:

Variable	Type	Description
AI	Continuous	Asymmetry index
Dx	Categorical (binary)	Diagnosis: schizophrenia or unaffected control
HAND	Categorical (binary)	Hand preference: right or non-right (left + ambidextrous)
ICV	Continuous	Intracranial volume
Scanner	Categorical (binary)	Optional covariate: If a site used multiple scanners to obtain images, *n*-1 binary dummy covariates (where *n* is the number of scanners in a given dataset) were added, to differentiate which scanner an individual's data came from.
AP-group	Categorical	Antipsychotic medication groups, tested as binary variables for between-group comparisons (see main text).
Clinical variable	Continuous	Schizophrenia-specific clinical variable. We included chlorpromazine-equivalent (CPZ) medication dose, age at onset, duration of illness, PANSS total score, PANSS positive symptom score, PANSS negative symptom score, SAPS score or SANS score.

Models to assess case-control differences

Primary model:

[1] AI ~ **Dx** + Age + Sex (+ Scanner)

Primary model with additional covariates:

[2] AI ~ **Dx** + Age + Sex + HAND (+ Scanner)

[3] AI ~ **Dx** + Age + Sex + ICV (+ Scanner)

[4] AI ~ **Dx** + Age + Sex + HAND + ICV (+ Scanner)

[5] AI ~ **Dx** + Age + Age^2 + Sex (+ Scanner)

Models to assess medication group differences

Antipsychotic medication between-group comparisons within affected individuals:

[6] AI ~ **AP-group** + Age + Sex (+ Scanner)

Models to assess correlations with clinical variables in affected individuals

[7] Linear model: AI ~ **Clinical variable** + Sex + Age (+ Scanner)

Partial correlation: $\rho(AI)(\textbf{Clinical variable})\cdot\{Sex, Age, (Scanner)\}$

Models to assess diagnosis-by-age and diagnosis-by-sex interactions, including correlations with age

[8] AI ~ Dx + Age + Sex + **Dx*Age +** (Scanner)

[8b] Linear model: AI ~ **Age** + Sex (+ Scanner)

Partial correlation: $\rho(AI)(\textbf{Age})\cdot\{Sex, (Scanner)\}$

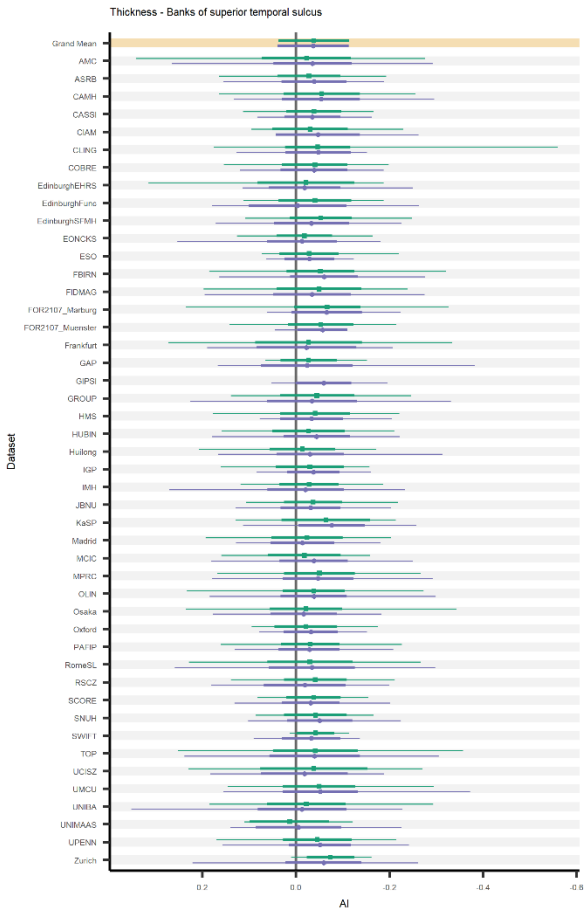
[9] AI ~ Dx + Age + Sex + **Dx*Sex** + (Scanner)

Supplementary figures

Figure S1 (page 6-14). Overall and per-dataset average and spread for cortical thickness asymmetries. For each cortical thickness asymmetry measure, the average in controls (green circles) and individuals affected with schizophrenia (purple squares) is shown. The top (highlighted) row contains the grand sample size-weighted mean and standard deviation (thick line segments). The other rows contain per-dataset averages, standard deviations and minimum and maximum values (indicated with thin line segments).

Figure S2 (page 15-23). Overall and per-dataset average and spread for cortical surface area asymmetries. For each cortical surface area asymmetry measure, the average in controls (green circles) and individuals affected with schizophrenia (purple squares) is shown. The top (highlighted) row contains the grand sample size-weighted mean and standard deviation (thick line segments). The other rows contain per-dataset averages, standard deviations and minimum and maximum values (indicated with thin line segments).

Figure S3 (page 24-25). Overall and per-dataset average and spread for subcortical volume asymmetries. For each subcortical volume asymmetry measure, the average in controls (green circles) and individuals affected with schizophrenia (purple squares) is shown. The top (highlighted) row contains the grand sample size-weighted mean and standard deviation (thick line segments). The other rows contain per-dataset averages, standard deviations and minimum and maximum values (indicated with thin line segments).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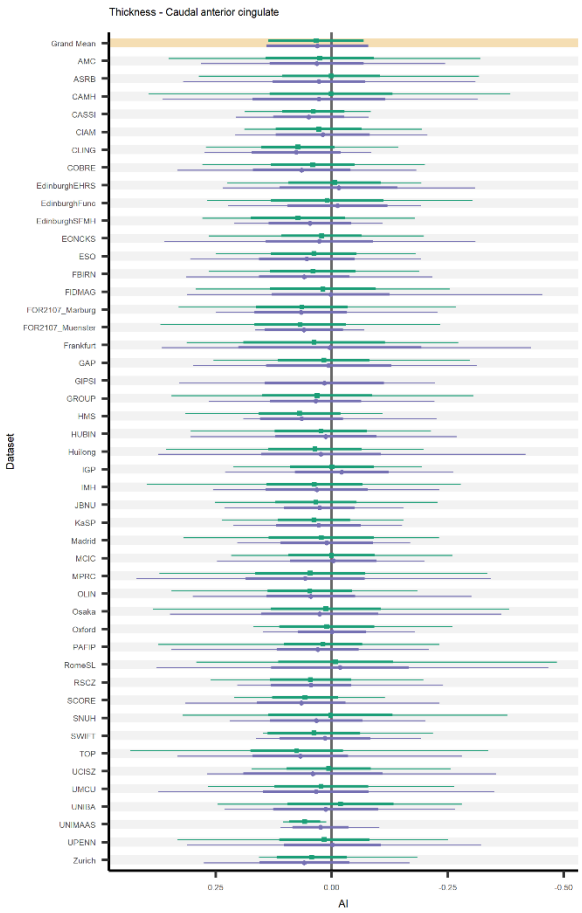
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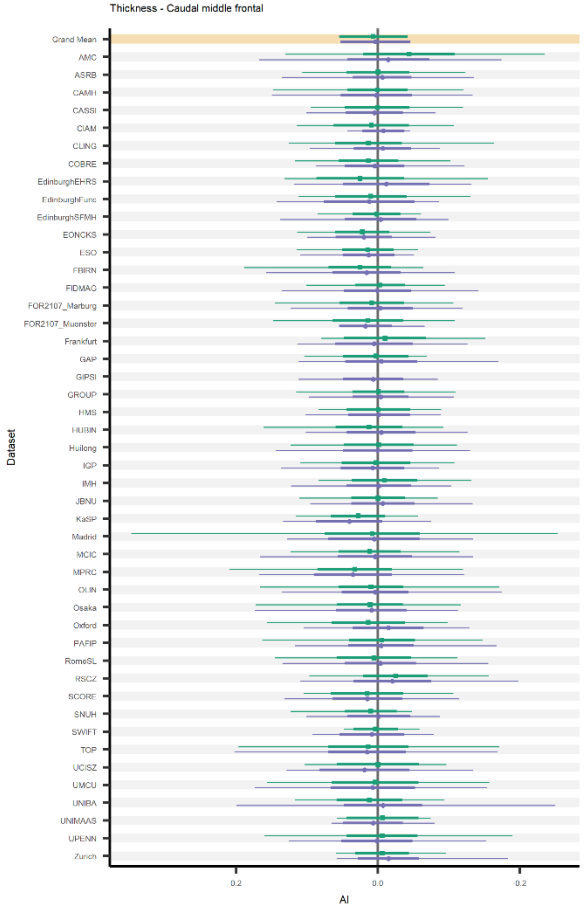
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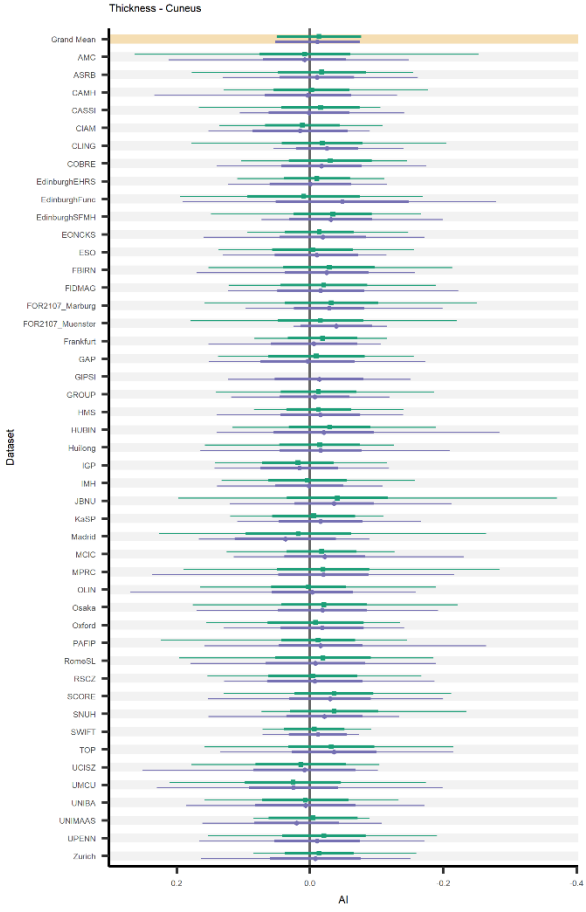
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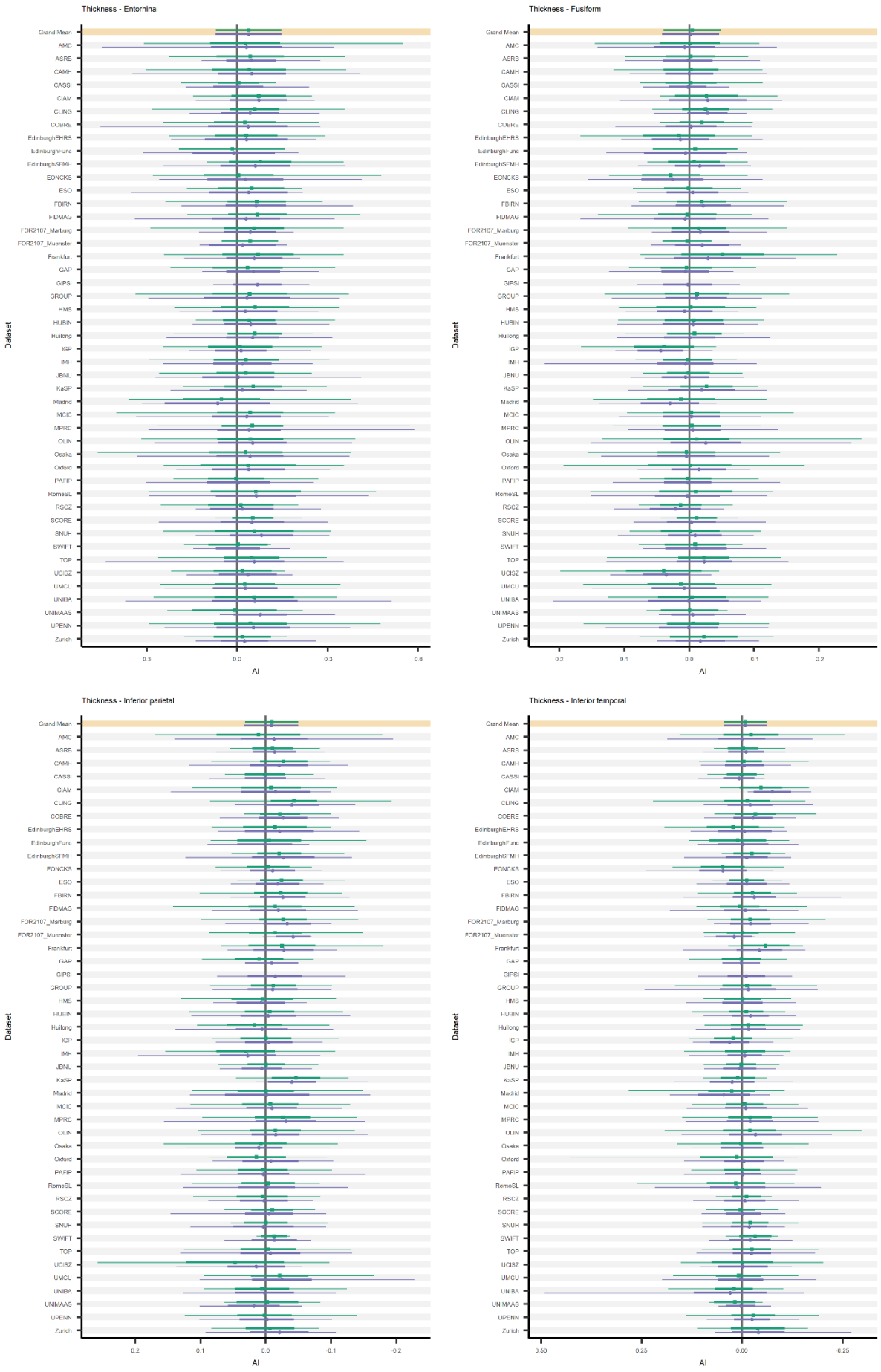
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Thickness - Fusiform
Thickness - Inferior parietal
Thickness - Inferior temporal
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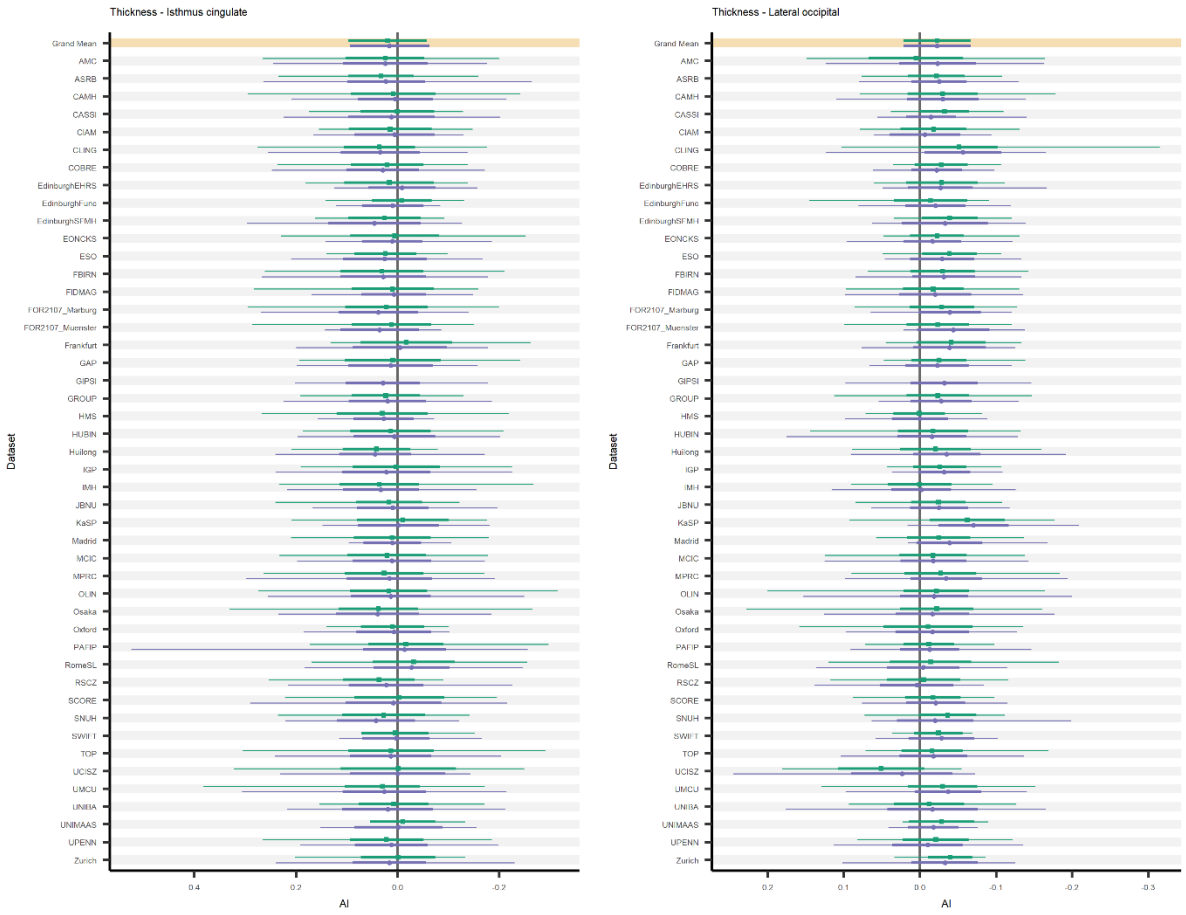
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Thickness - Lateral occipital
Thickness - Lateral orbitofrontal
Thickness - Lingual
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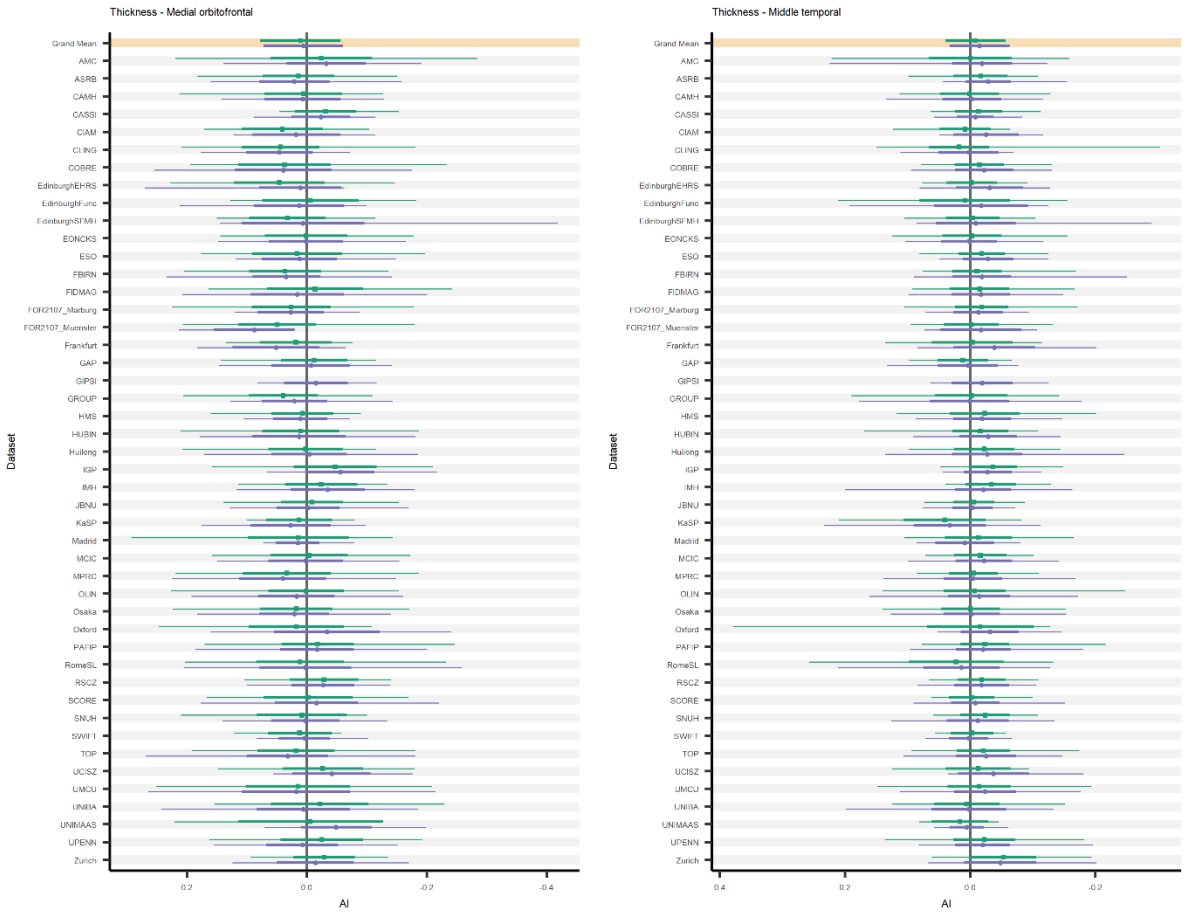
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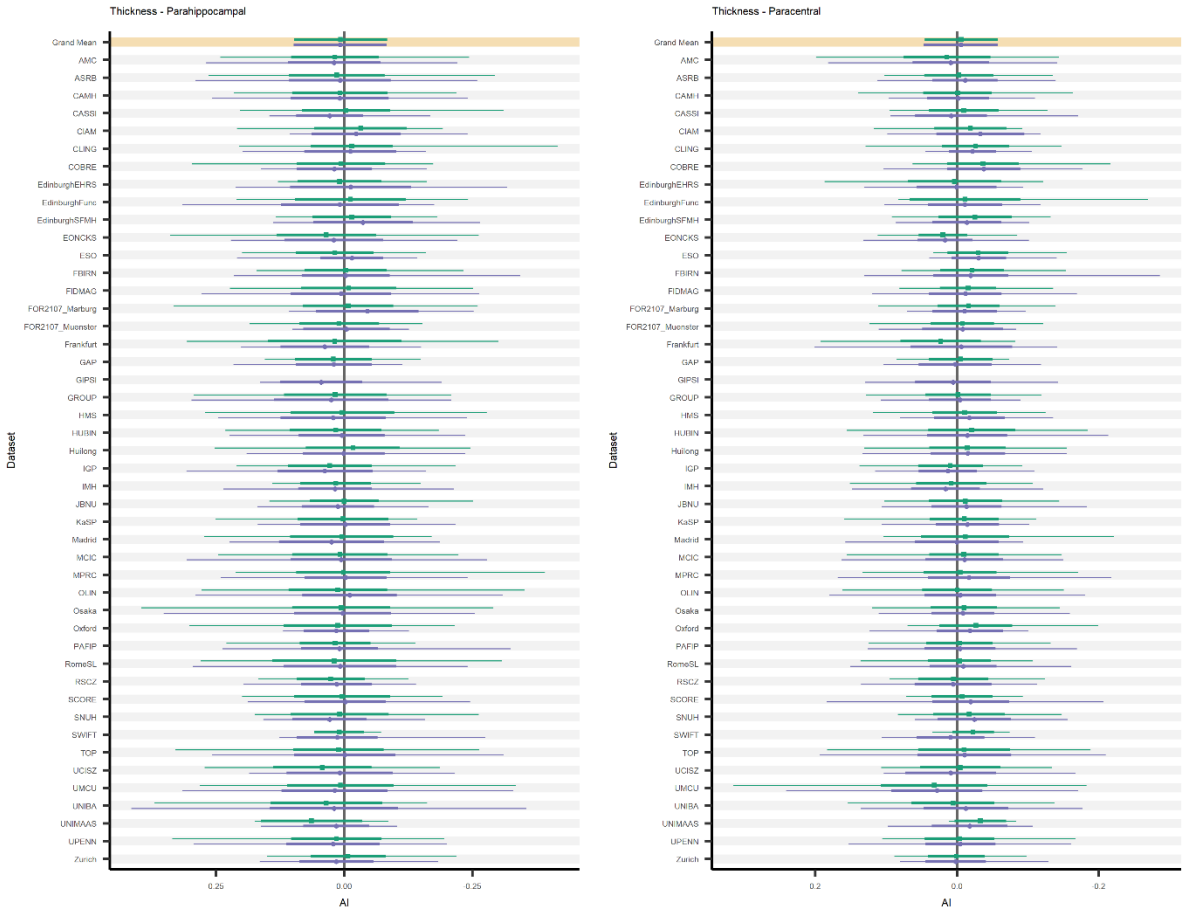
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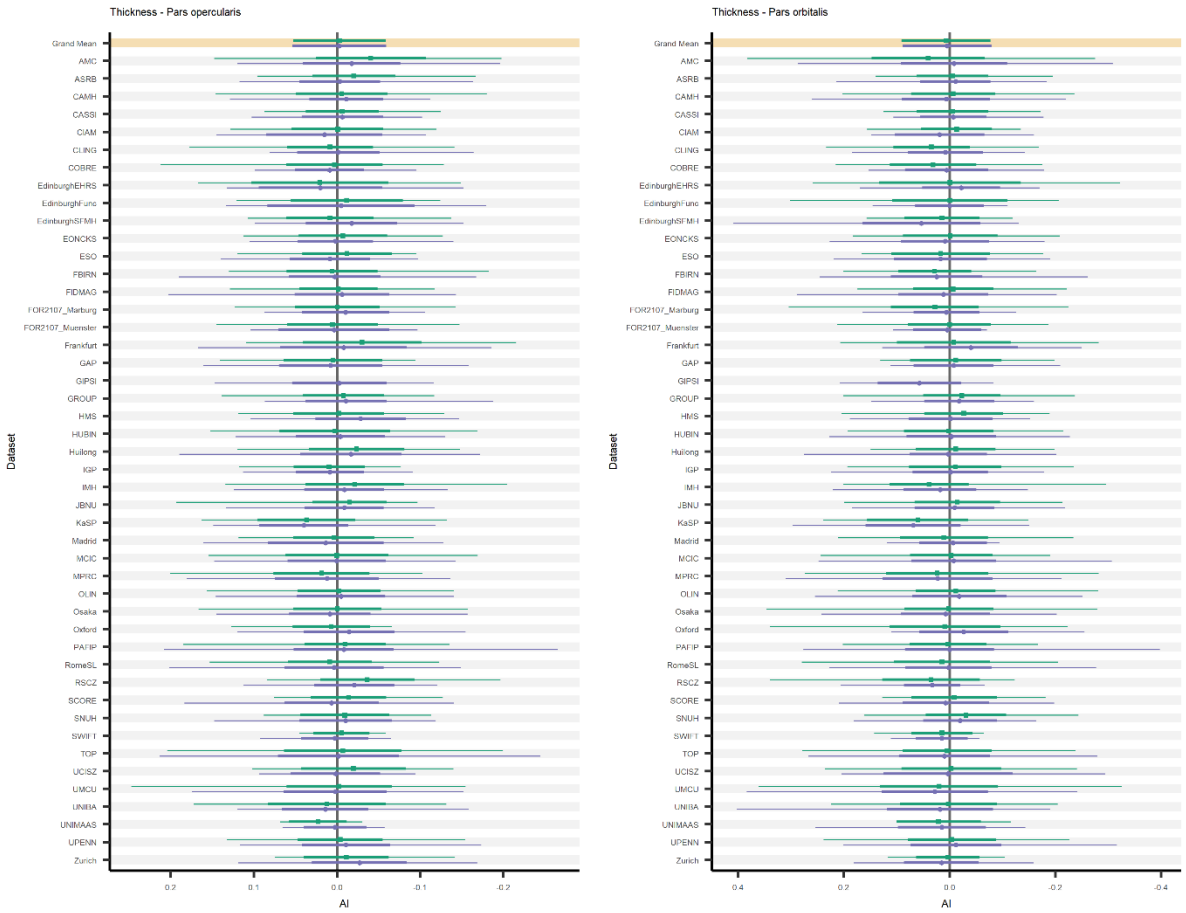
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Thickness - Pars orbitalis
Thickness - Pars triangularis
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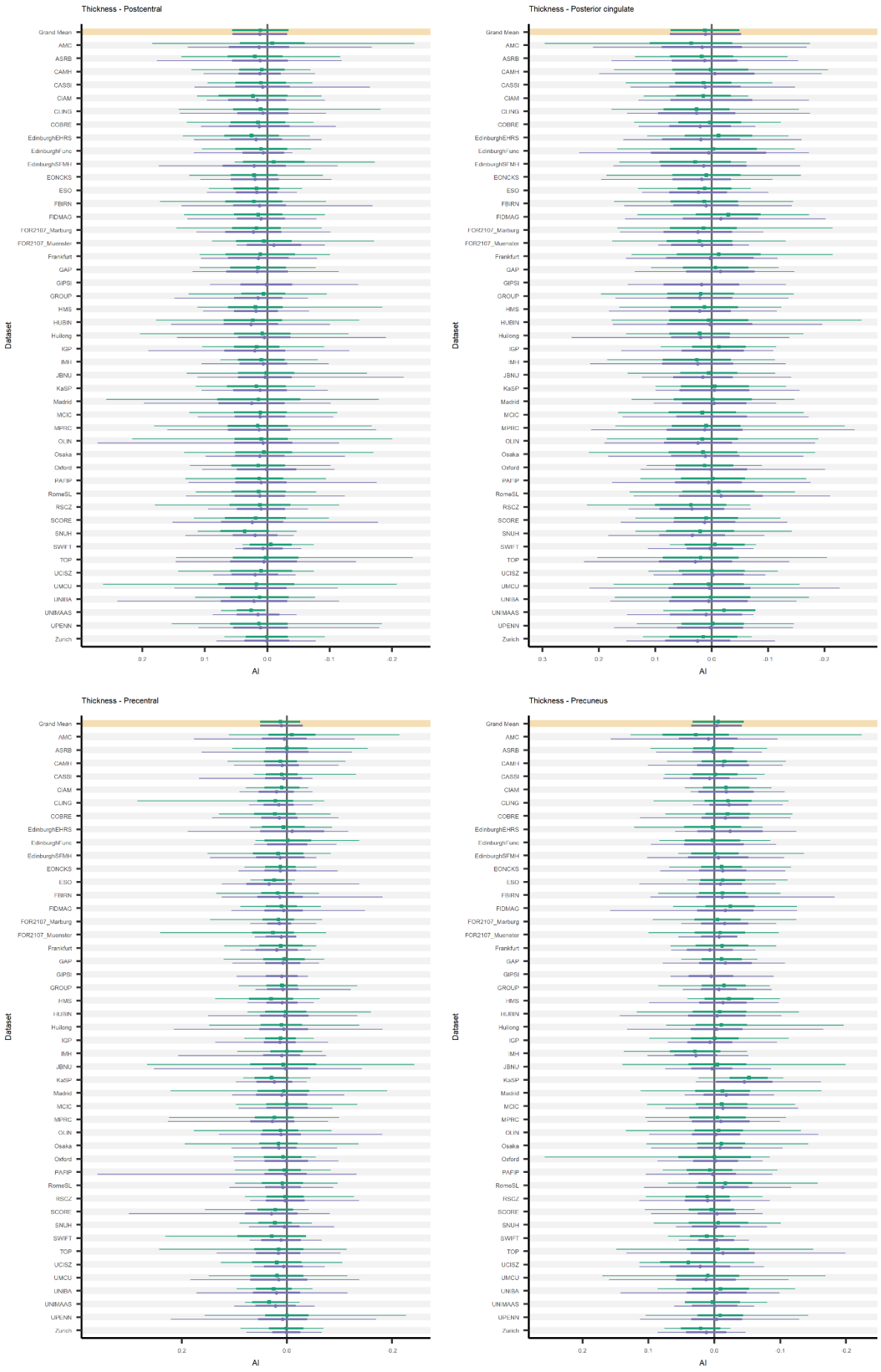
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Thickness - Precentral
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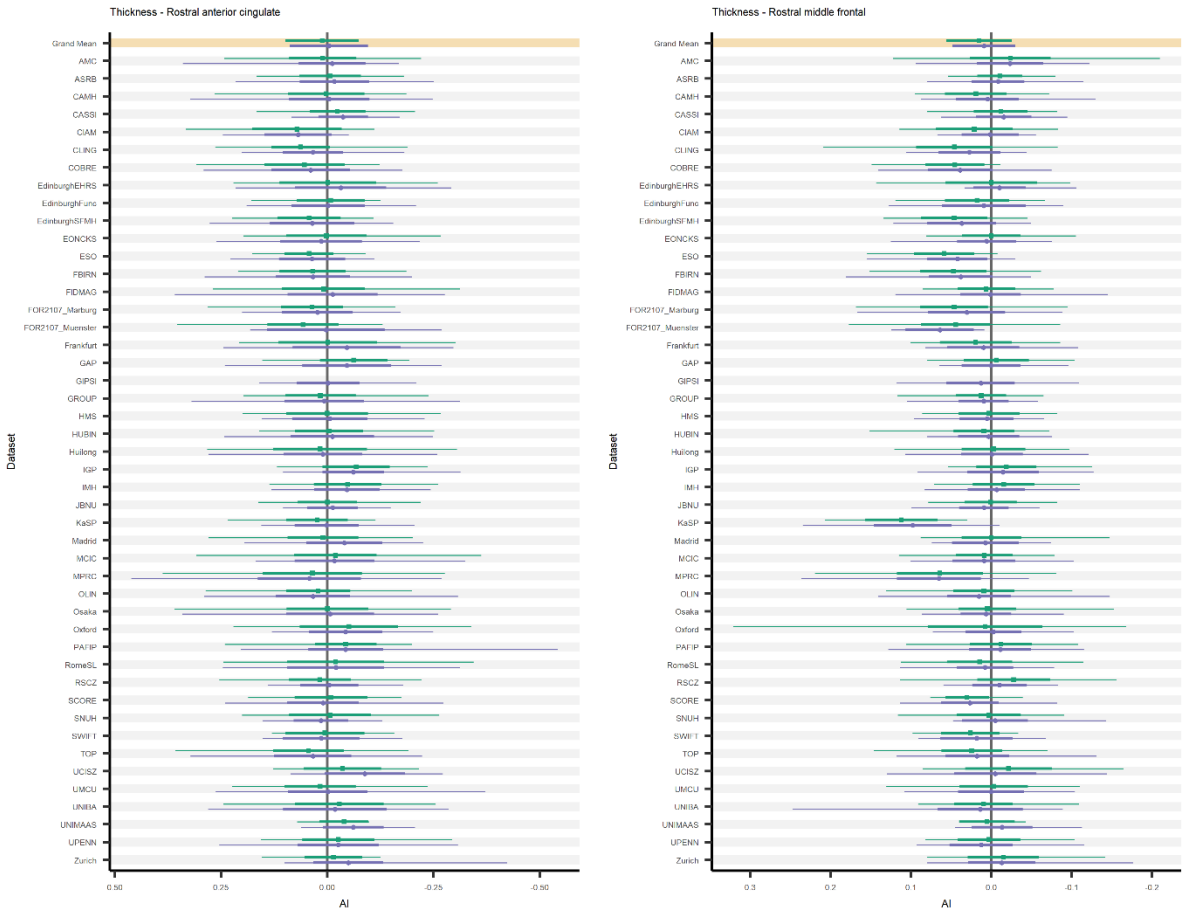
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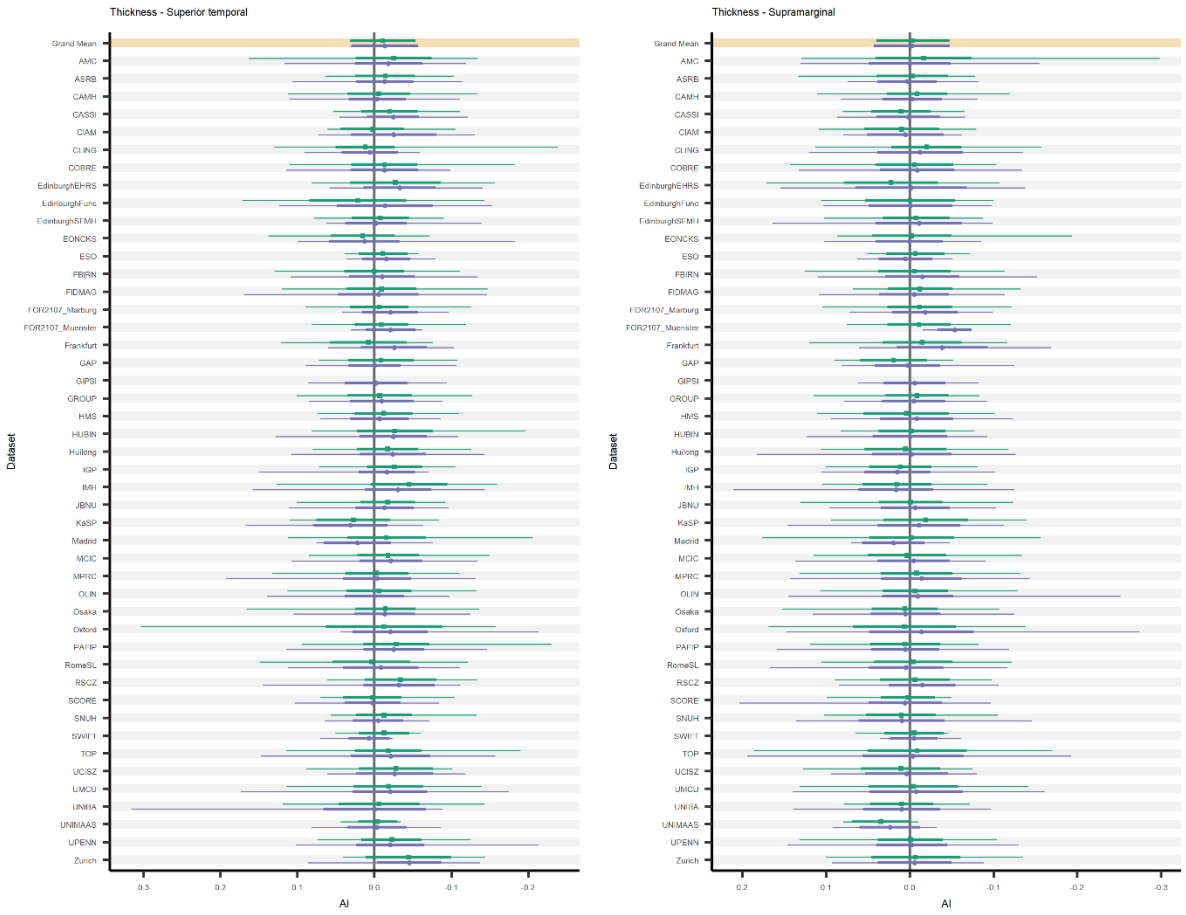
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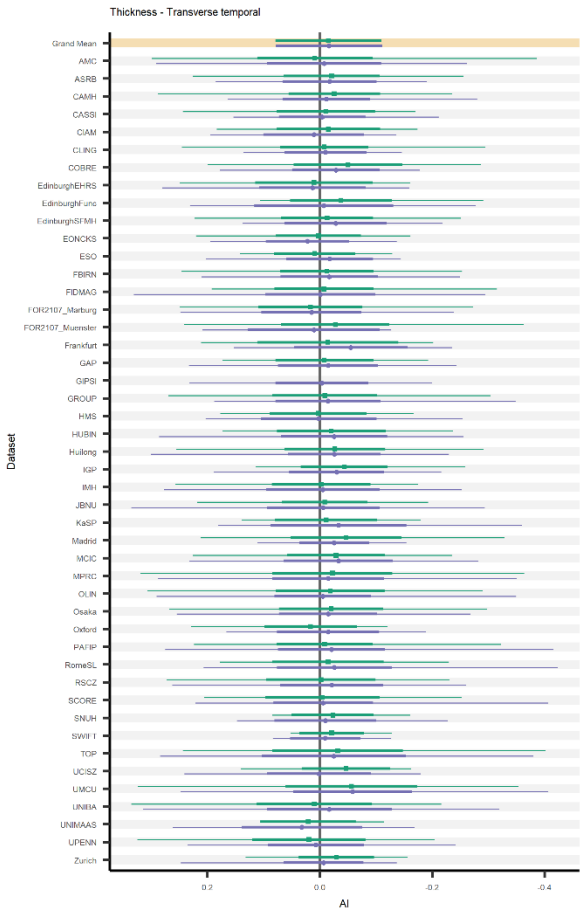
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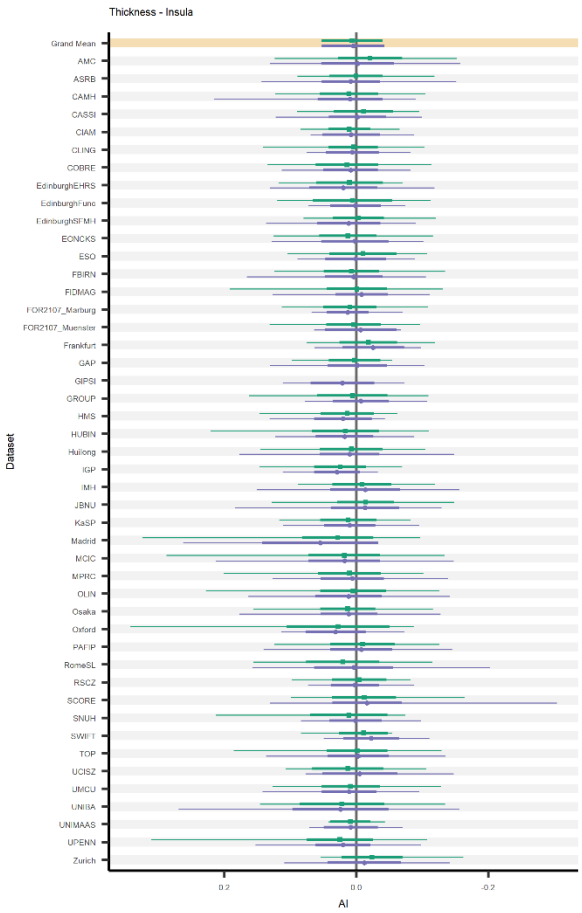
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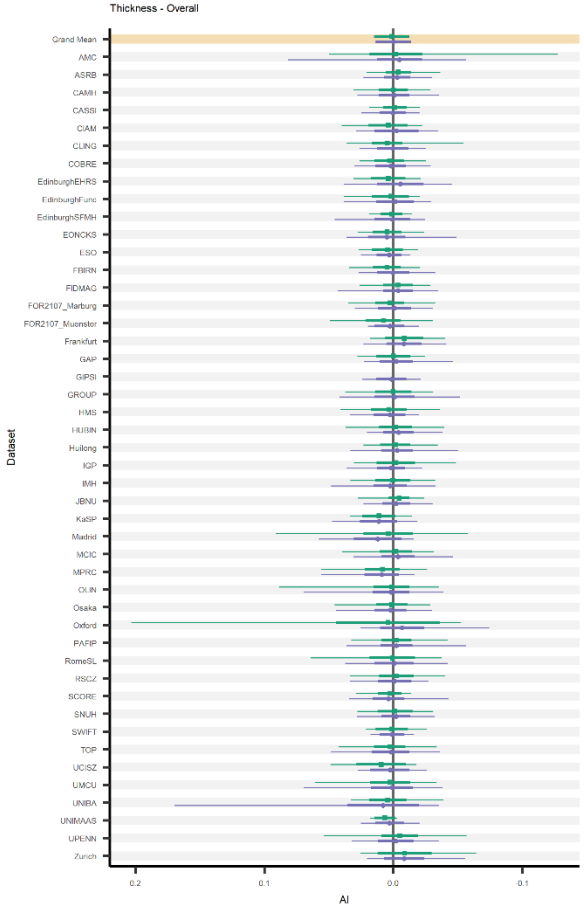
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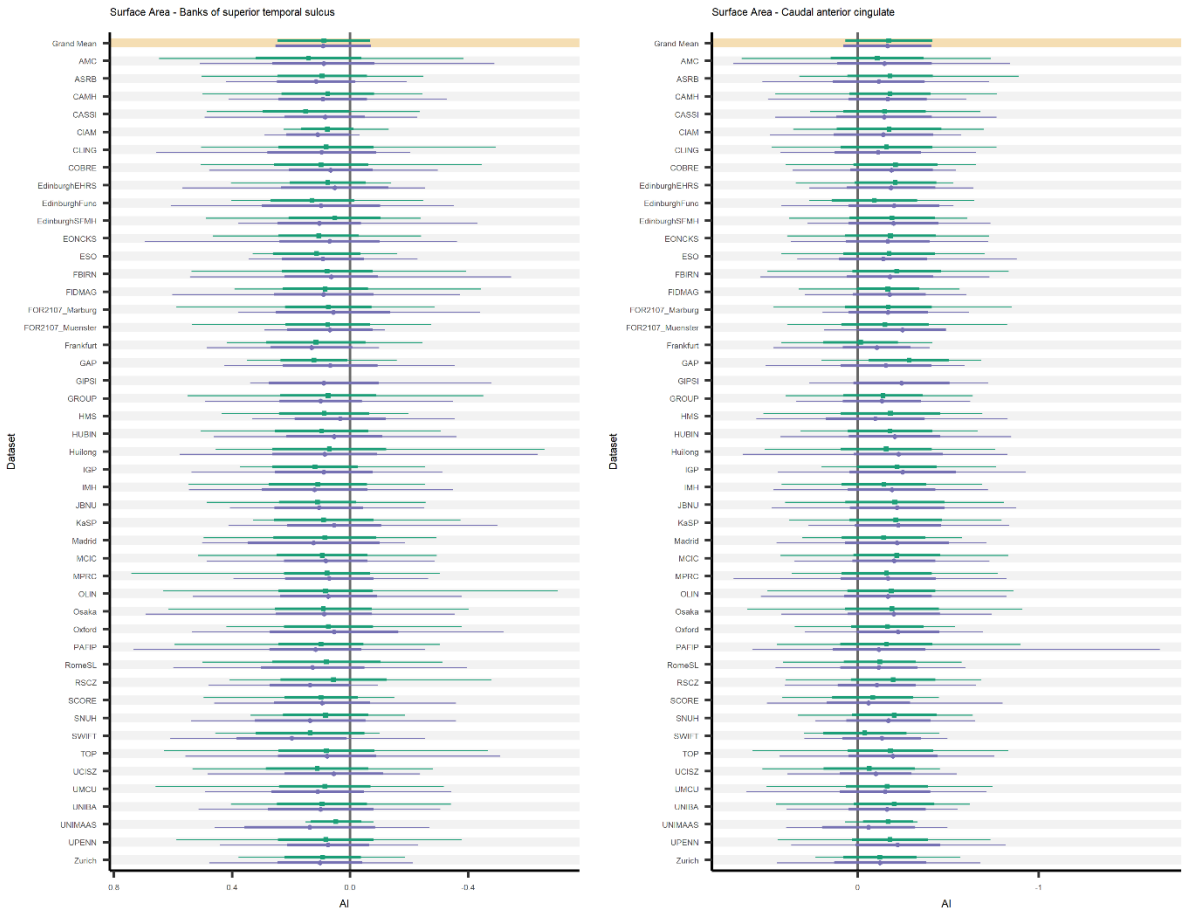
Surface Area - Banks of superior temporal sulcus
Surface Area - Caudal anterior cingulate
Surface Area - Caudal middle frontal
Surface Area - Cuneus
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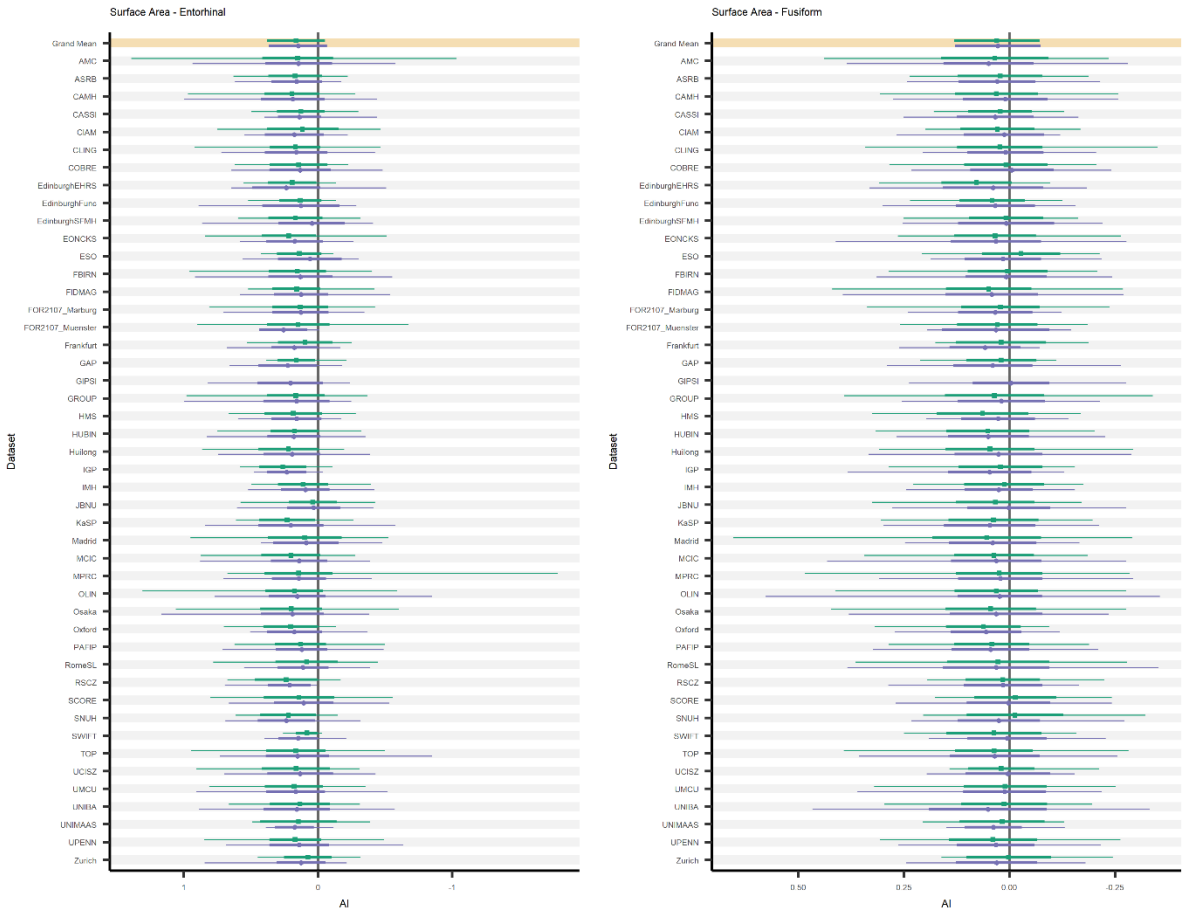
Surface Area - Entorhinal
Surface Area - Fusiform
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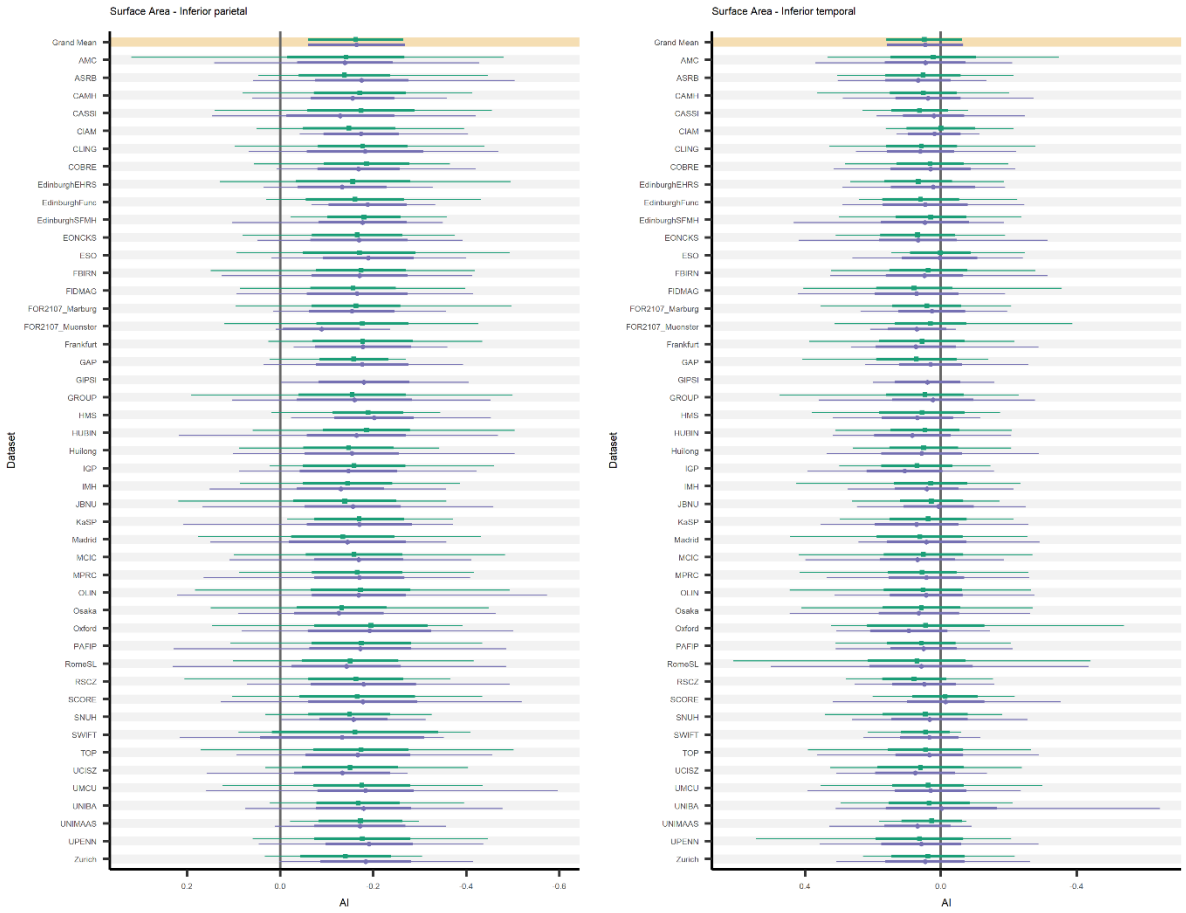
Surface Area - Inferior parietal
Surface Area - Inferior temporal
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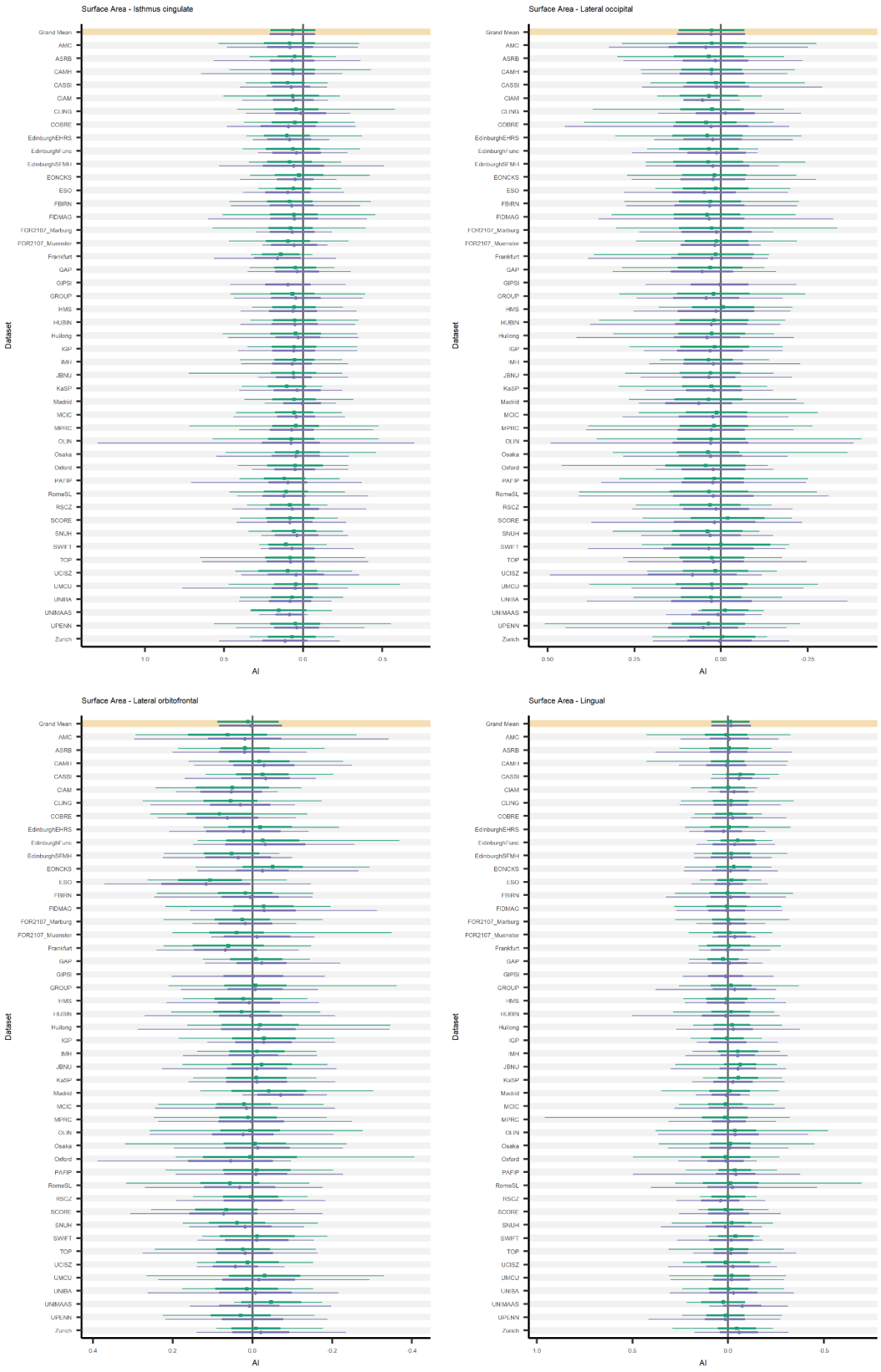
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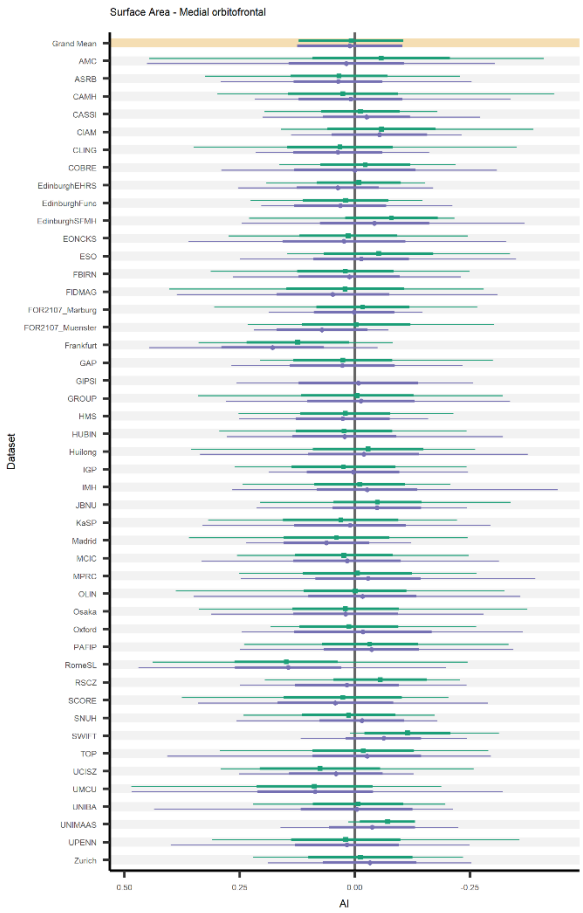
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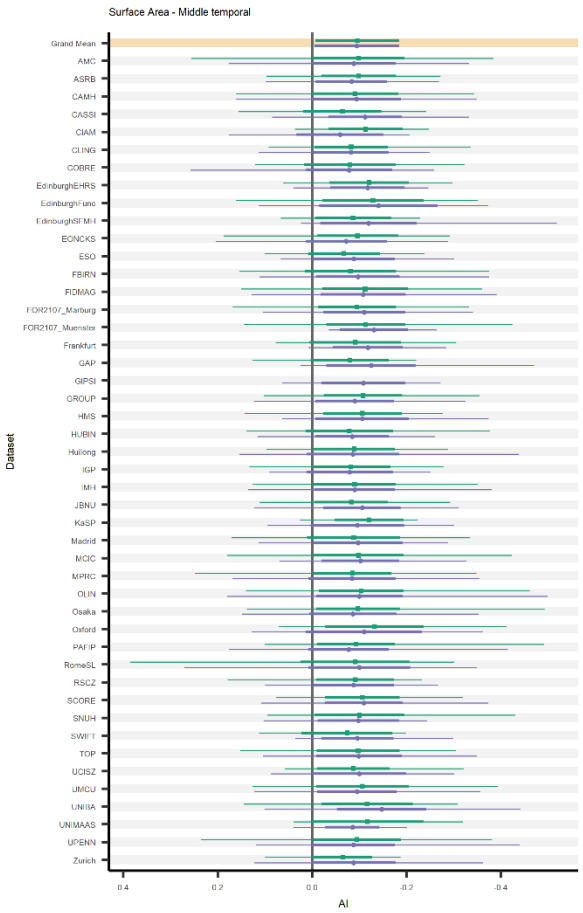
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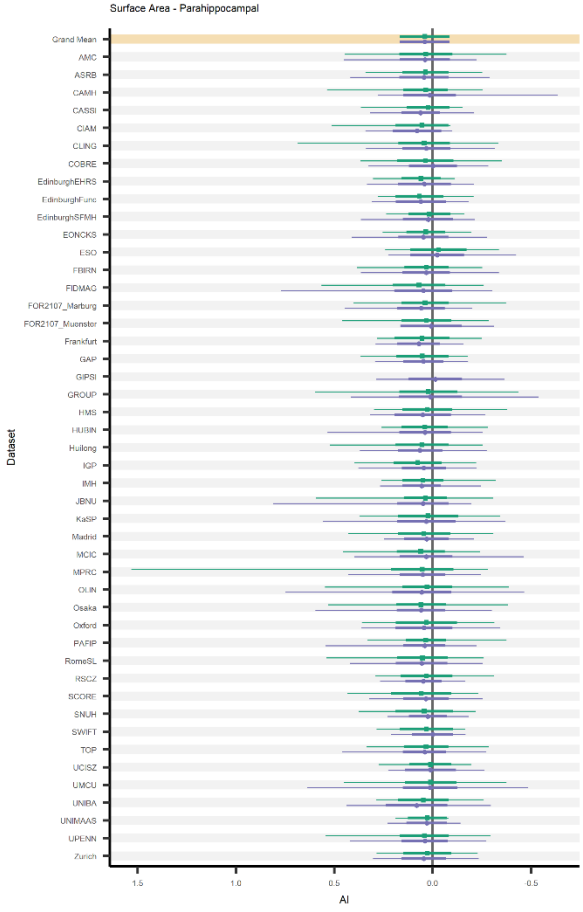
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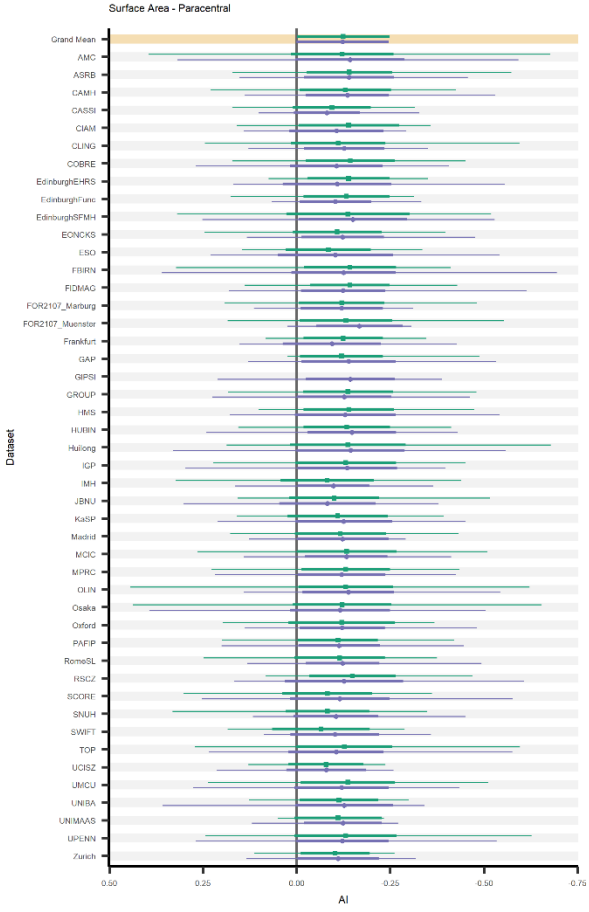
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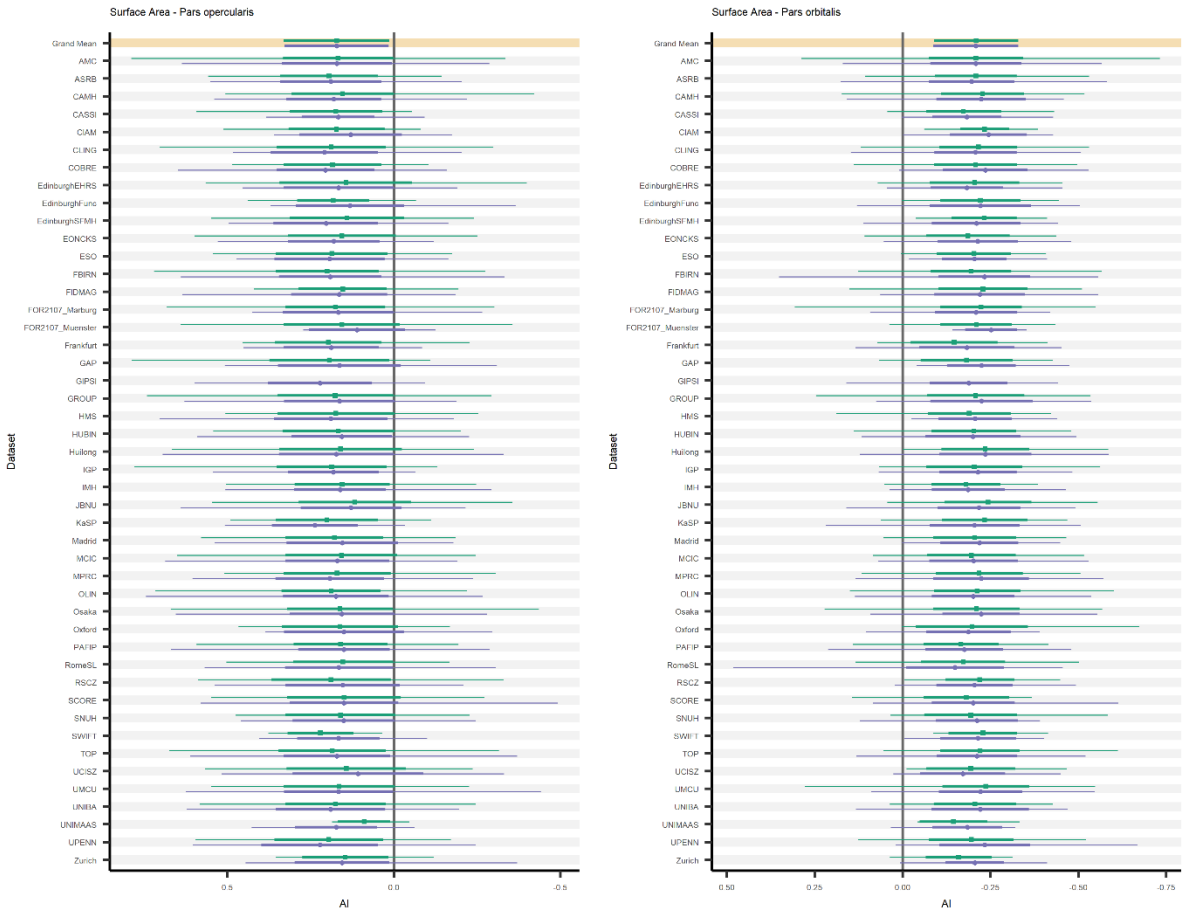
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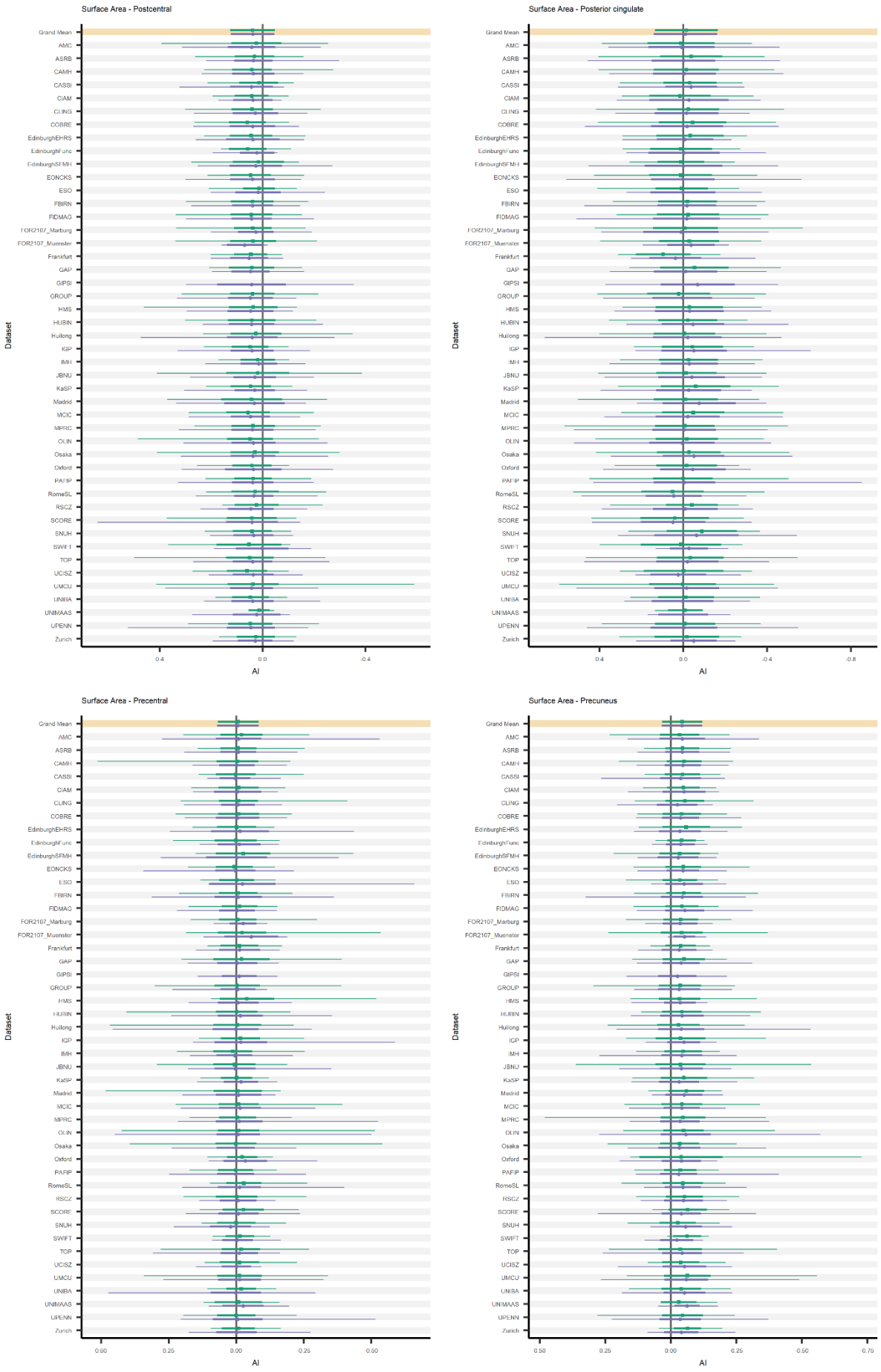
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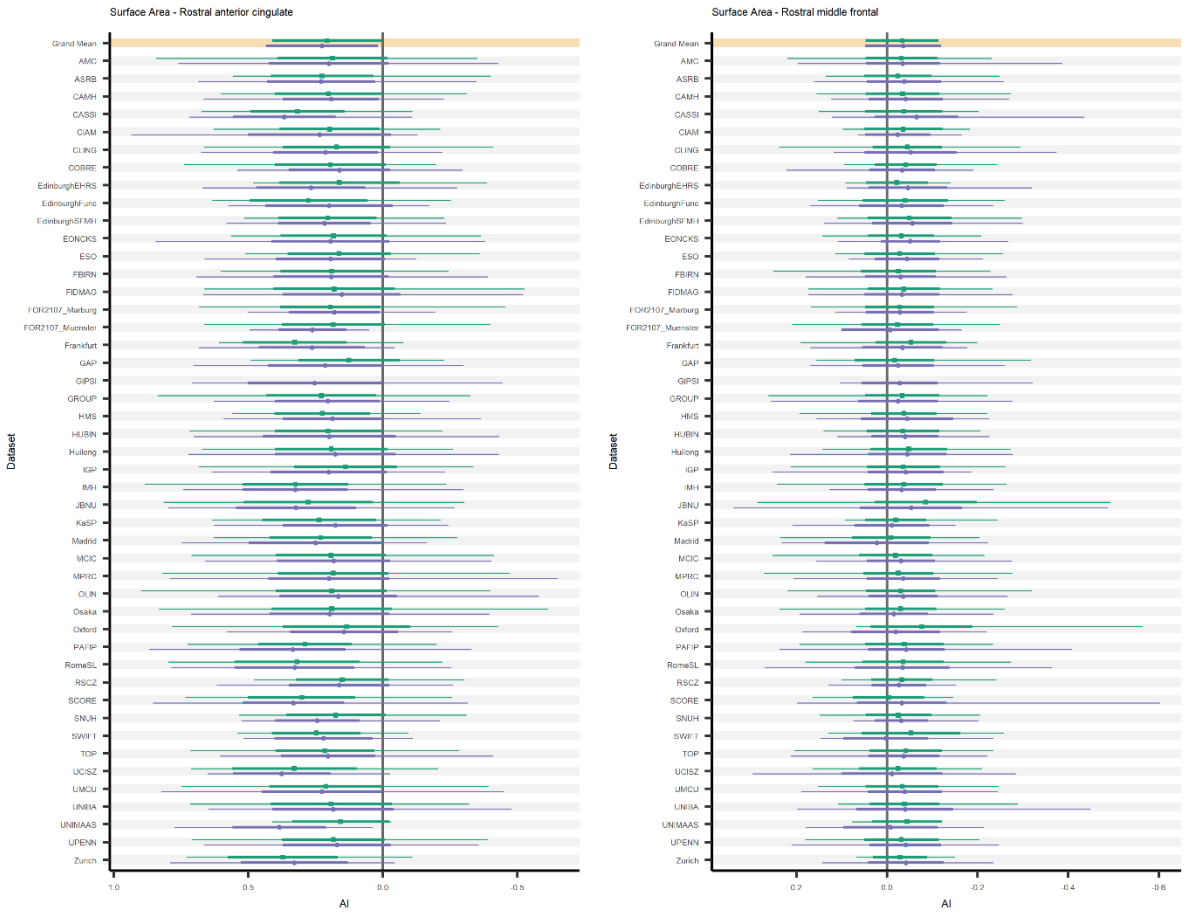
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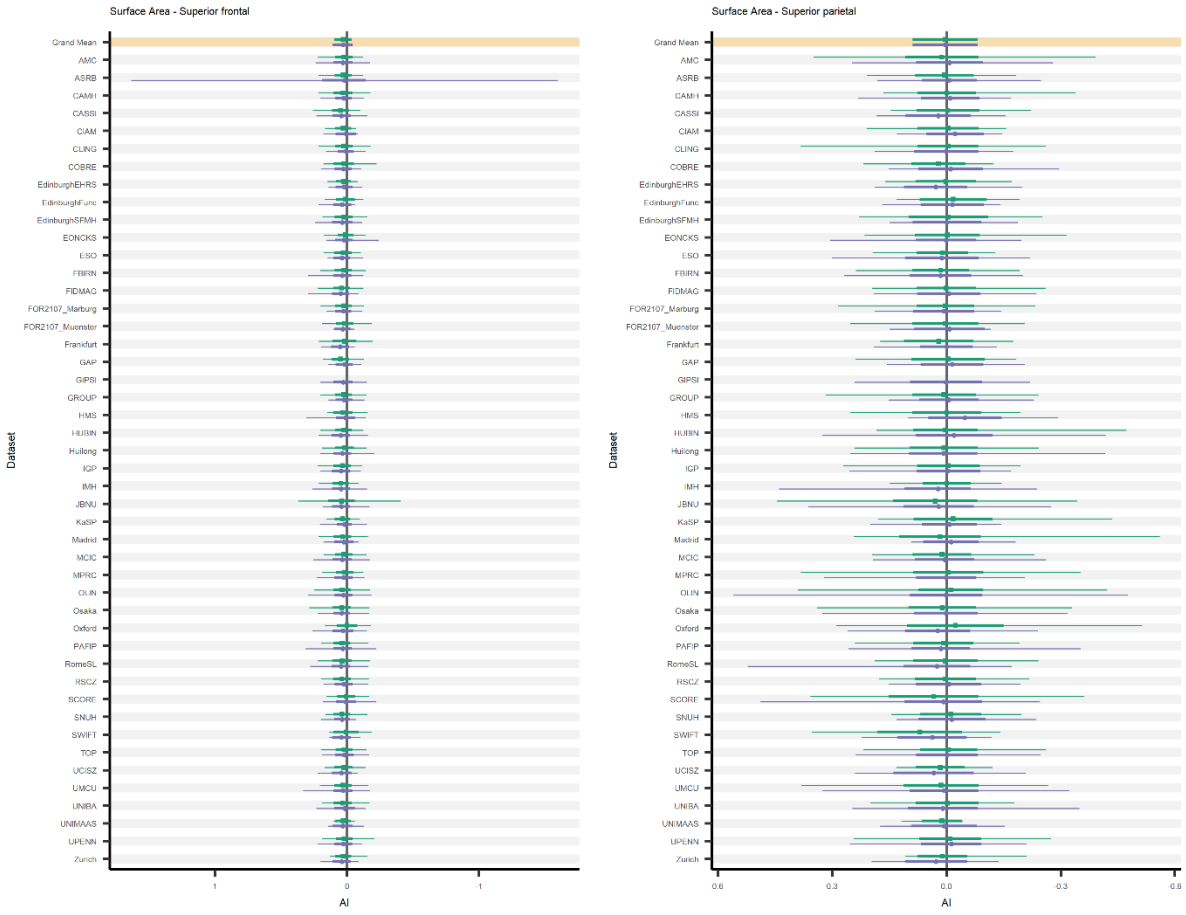
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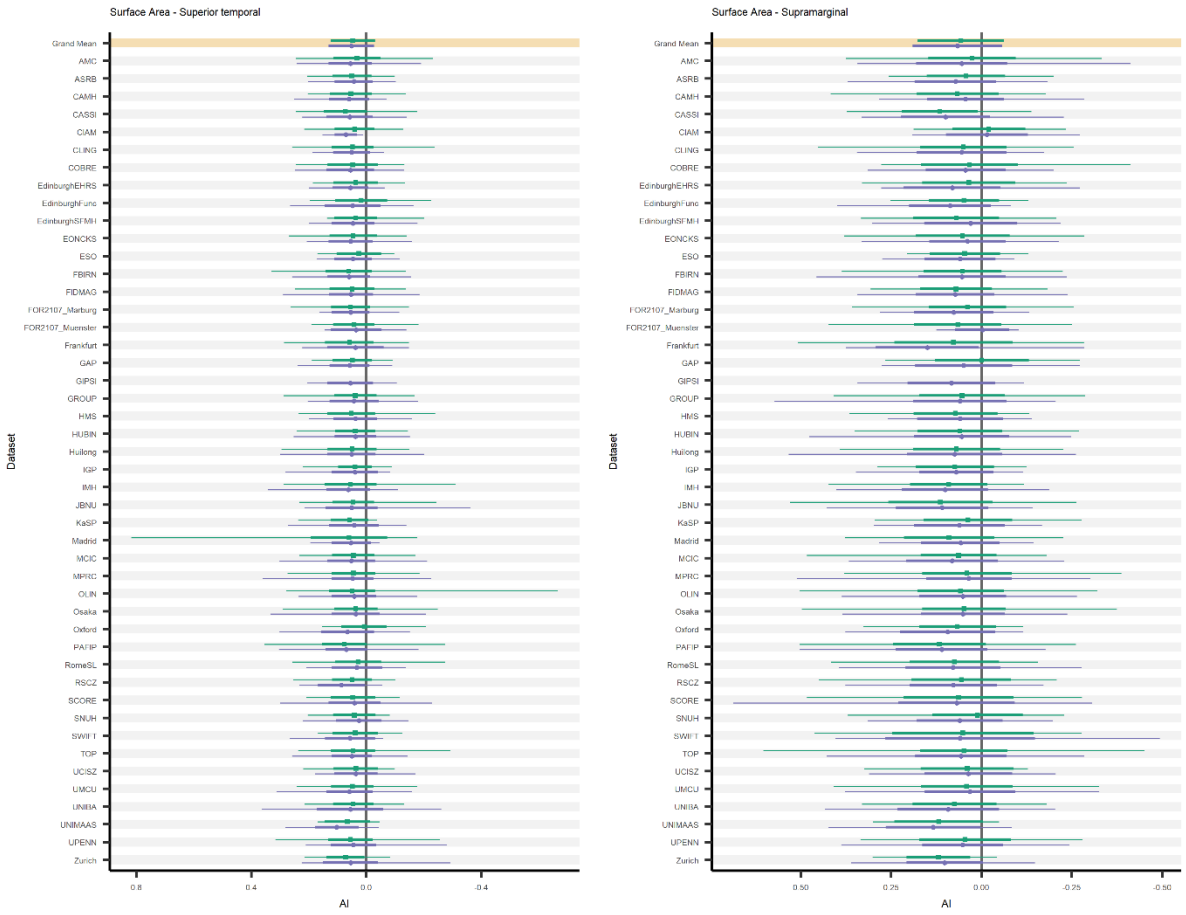
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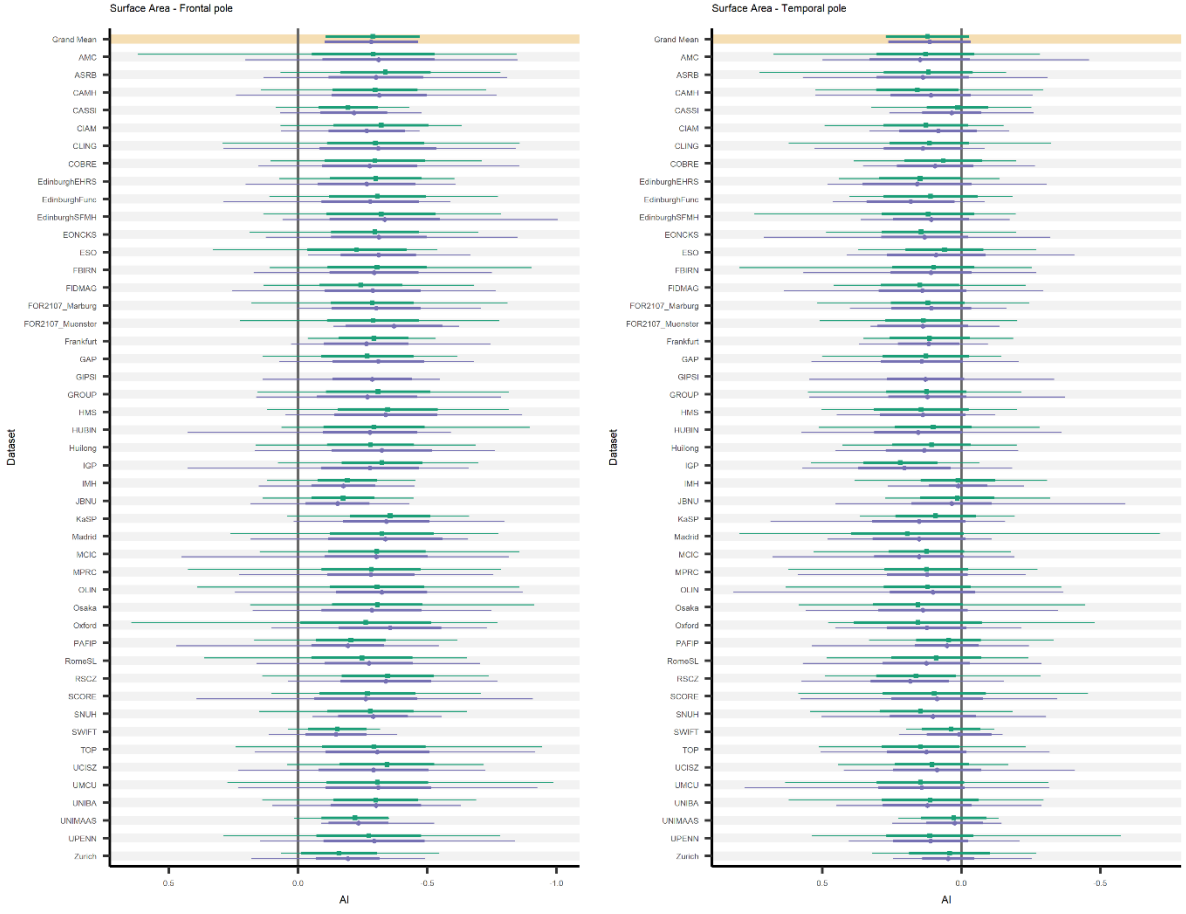
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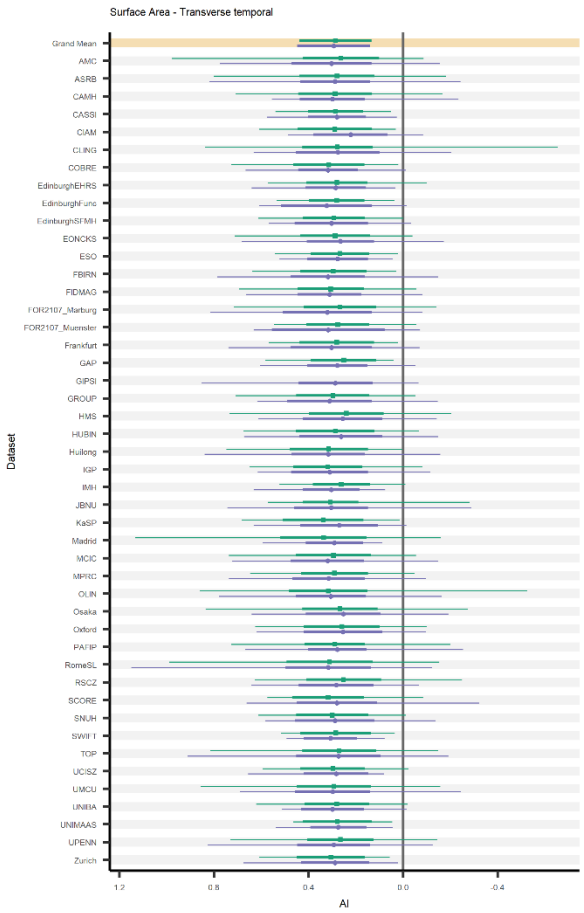
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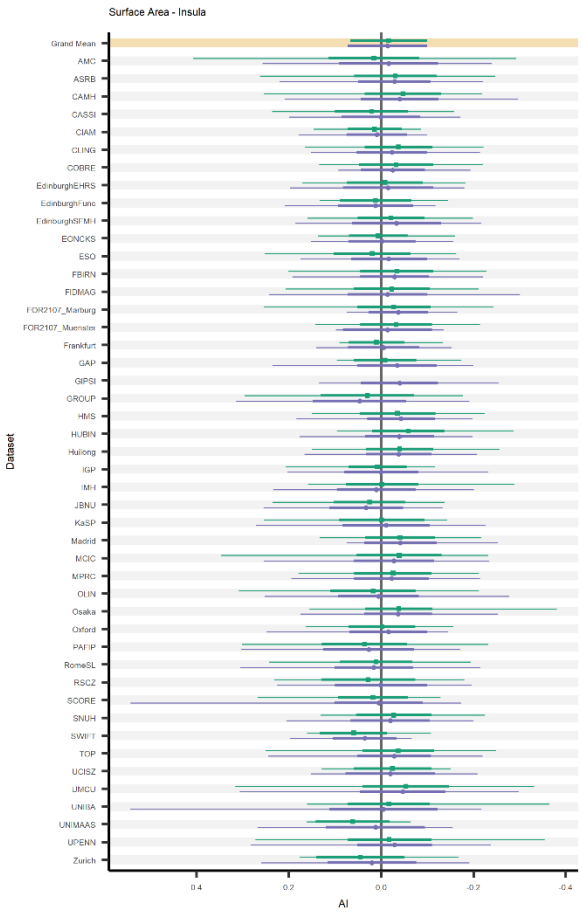
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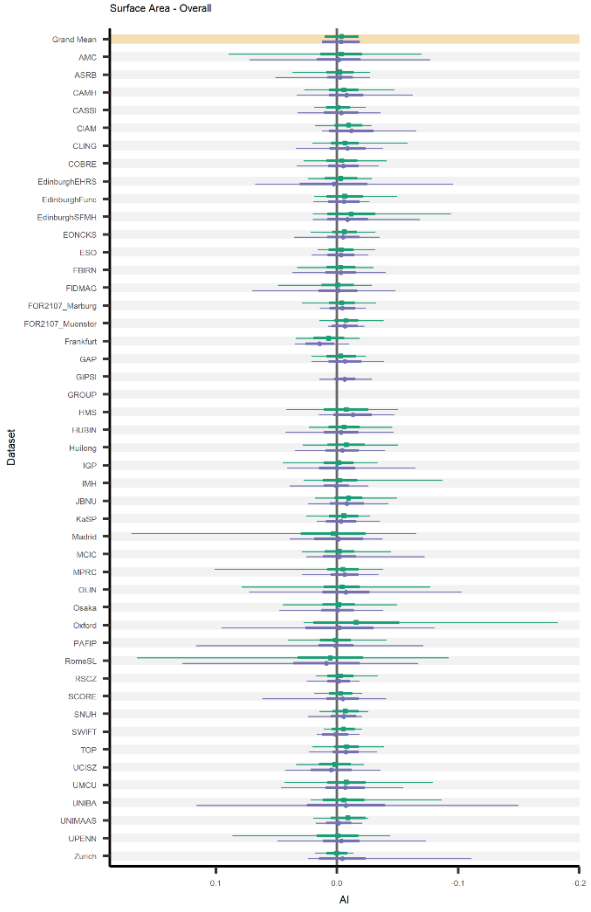
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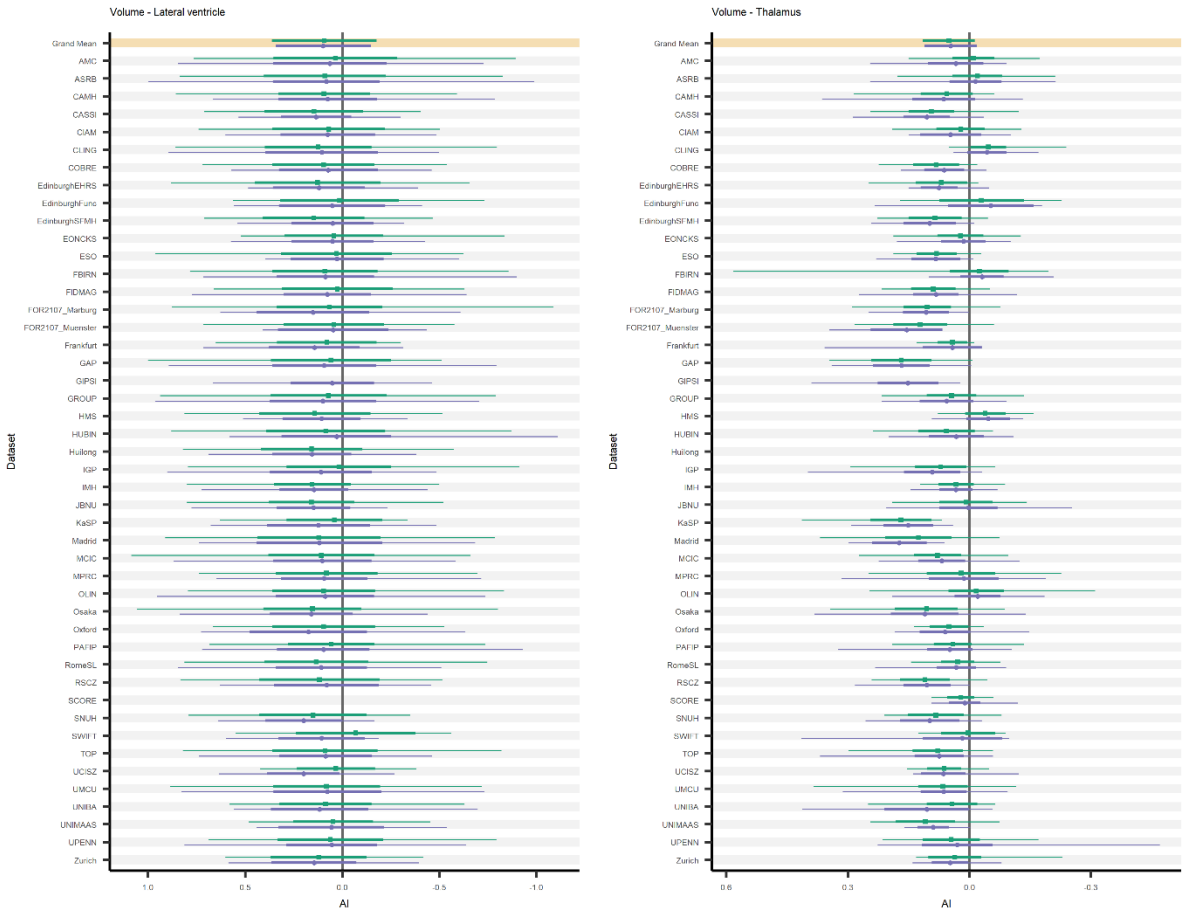
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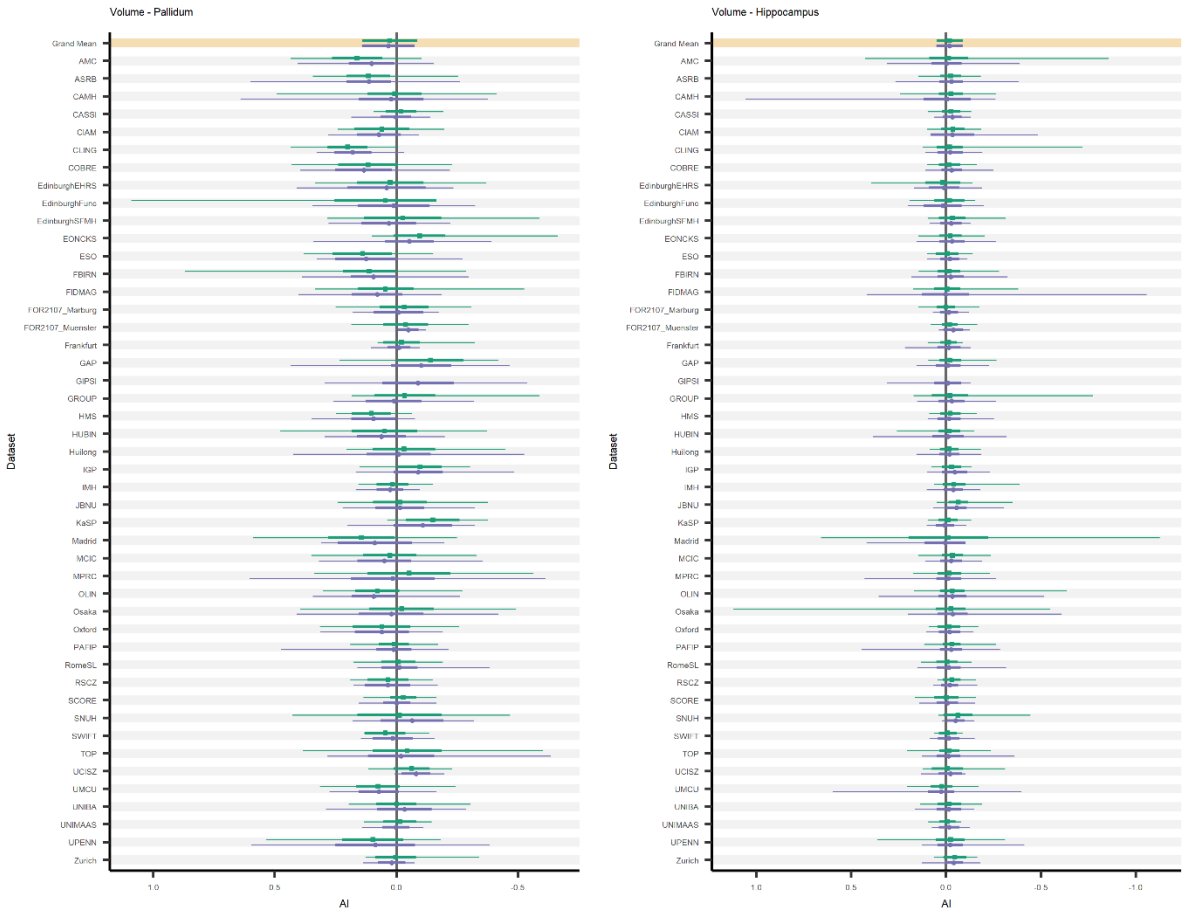
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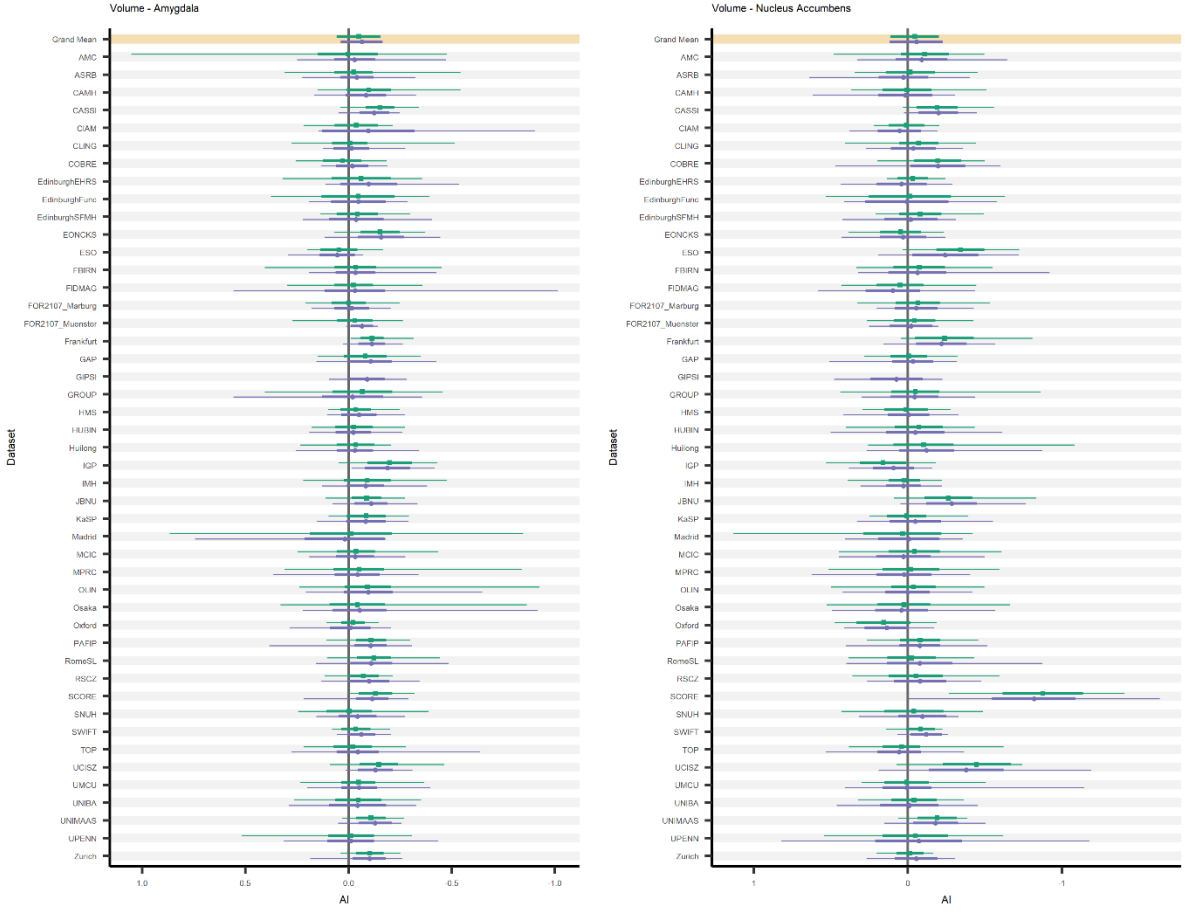
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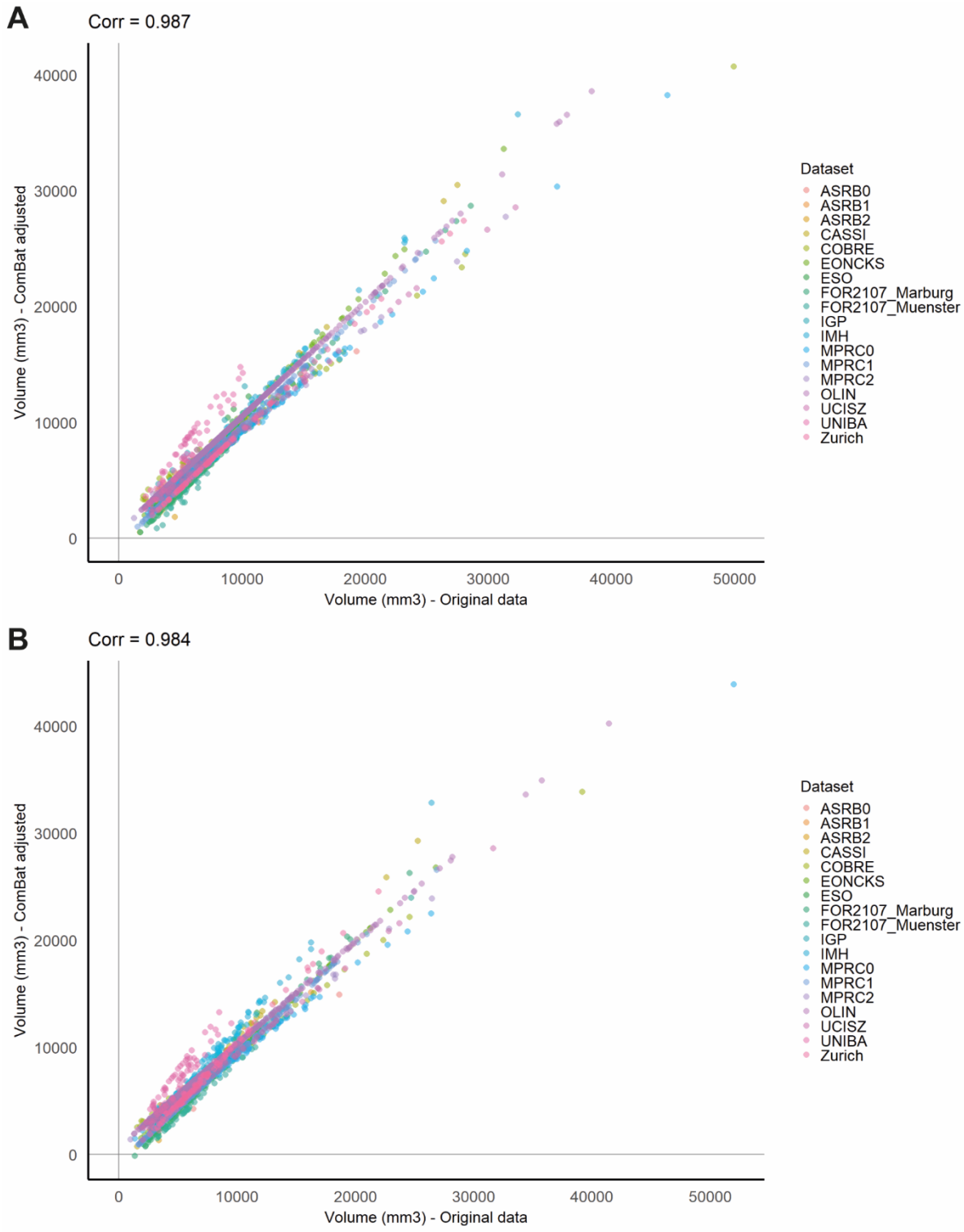


Figure S4. Original and ComBat adjusted lateral ventricle volume measurements. Original lateral ventricle volumes (x-axis) versus ComBat adjusted measurements (y-axis) for the left **(A)** and right **(B)** hemispheres are shown for individuals across 14 datasets (color-coded, two datasets – ASRB and MPRC – are split because of multiple scanners. Correlations (Corr) between original and ComBat adjusted measurements are shown above each figure. One subject from the FOR2107 Marburg dataset had a slightly negative adjusted right lateral ventricle volume and was therefore excluded.

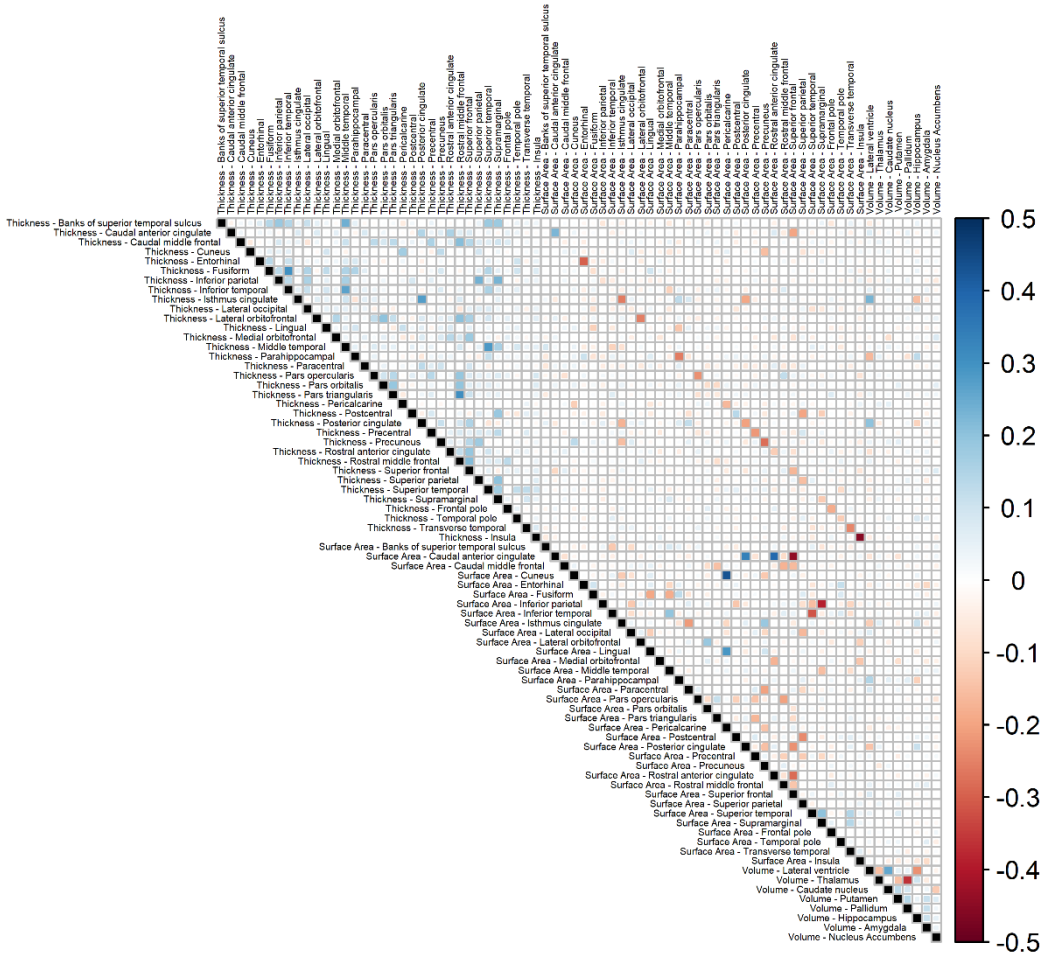


Figure S5. Correlations between structural asymmetries in the 14 datasets available for multivariate analysis (i.e. where individual-level data were available to the central analysis team). The correlations between AIs are shown at the intersections of rows and columns. Positive correlations are shown in blue shades, negative correlations are shown in red shades. Figure generated using the *corrplot* package in R (https://github.com/taiyun/corrplot).

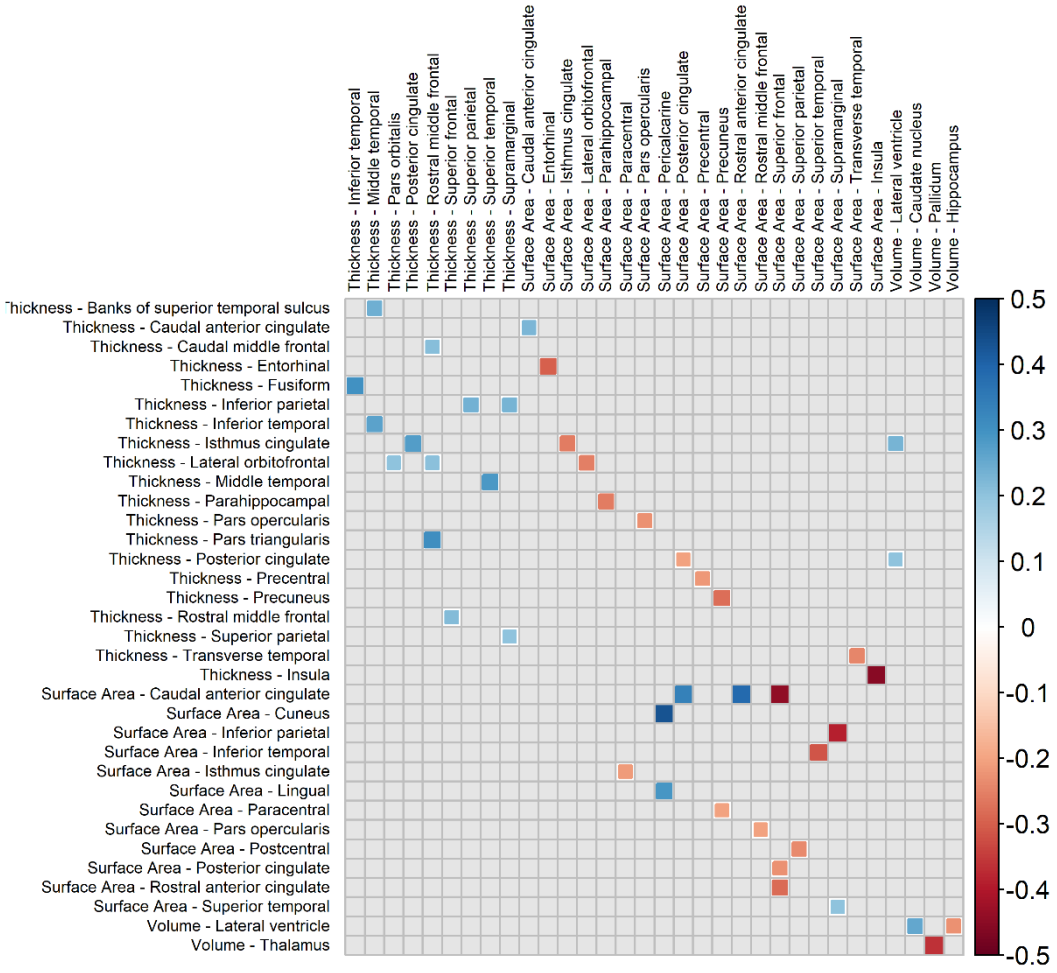


Figure S6. Correlations > 0.2 between structural asymmetries in the 14 datasets available for multivariate analysis (i.e. where individual-level data were available to the central analysis team). The correlations between AIs are shown at the intersections of rows and columns. Only correlations > 0.2 are shown and structural asymmetries not having any such large correlations are excluded from the matrix (i.e. this figure shows a subset of the same correlation matrix as in Figure S4, to aid in visualization of the larger correlations only). Positive correlations are shown in blue shades, negative correlations are shown in red shades. Figure generated using the *corrplot* package in R (https://github.com/taiyun/corrplot).

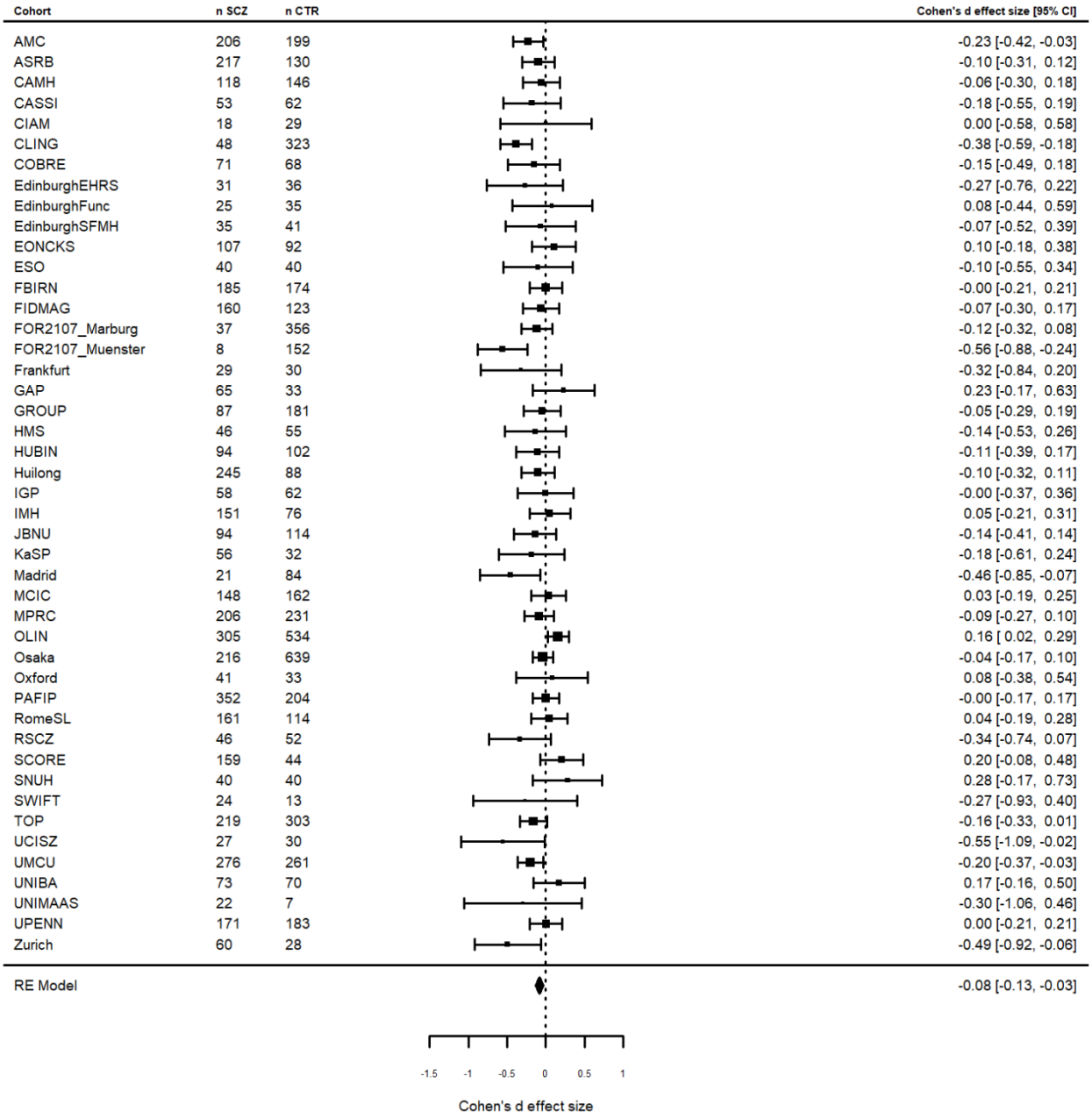


Figure S7. Forest plot for random effects meta-analysis of rostral anterior cingulate thickness asymmetry differences between schizophrenia individuals and unaffected controls. Per-dataset effect sizes, including confidence intervals, and sample sizes (n SCZ: number of schizophrenia individuals; n CTR: number of unaffected controls) are shown. The sizes of the dots represent the dataset sample sizes. The diamond shows the meta-analyzed effect.

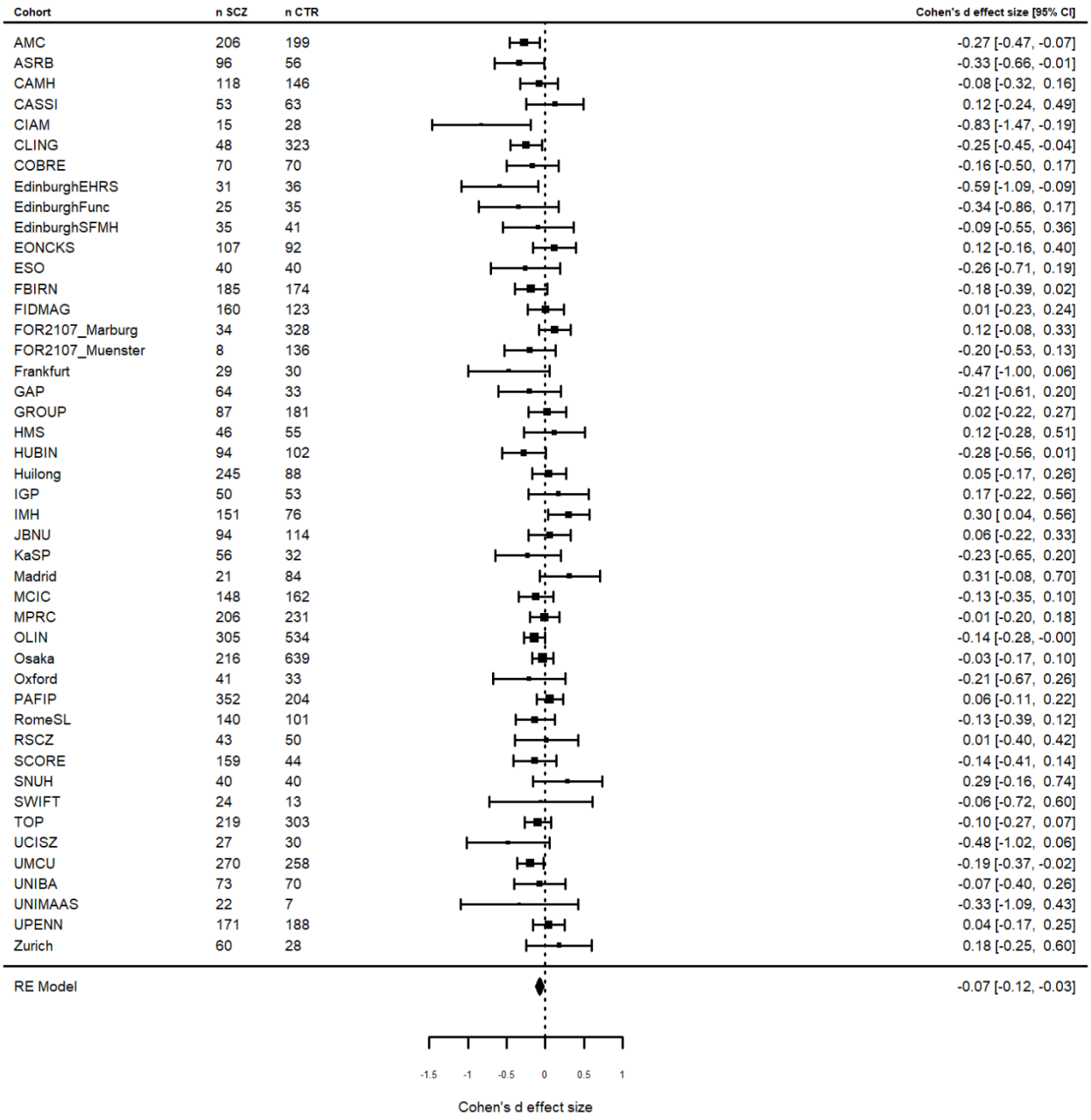


Figure S8. Forest plot for random effects meta-analysis of middle temporal gyrus thickness asymmetry differences between schizophrenia individuals and unaffected controls. Per-dataset effect sizes, including confidence intervals, and sample sizes (n SCZ: number of schizophrenia individuals; n CTR: number of unaffected controls) are shown. The sizes of the dots represent the dataset sample sizes. The diamond shows the meta-analyzed effect.

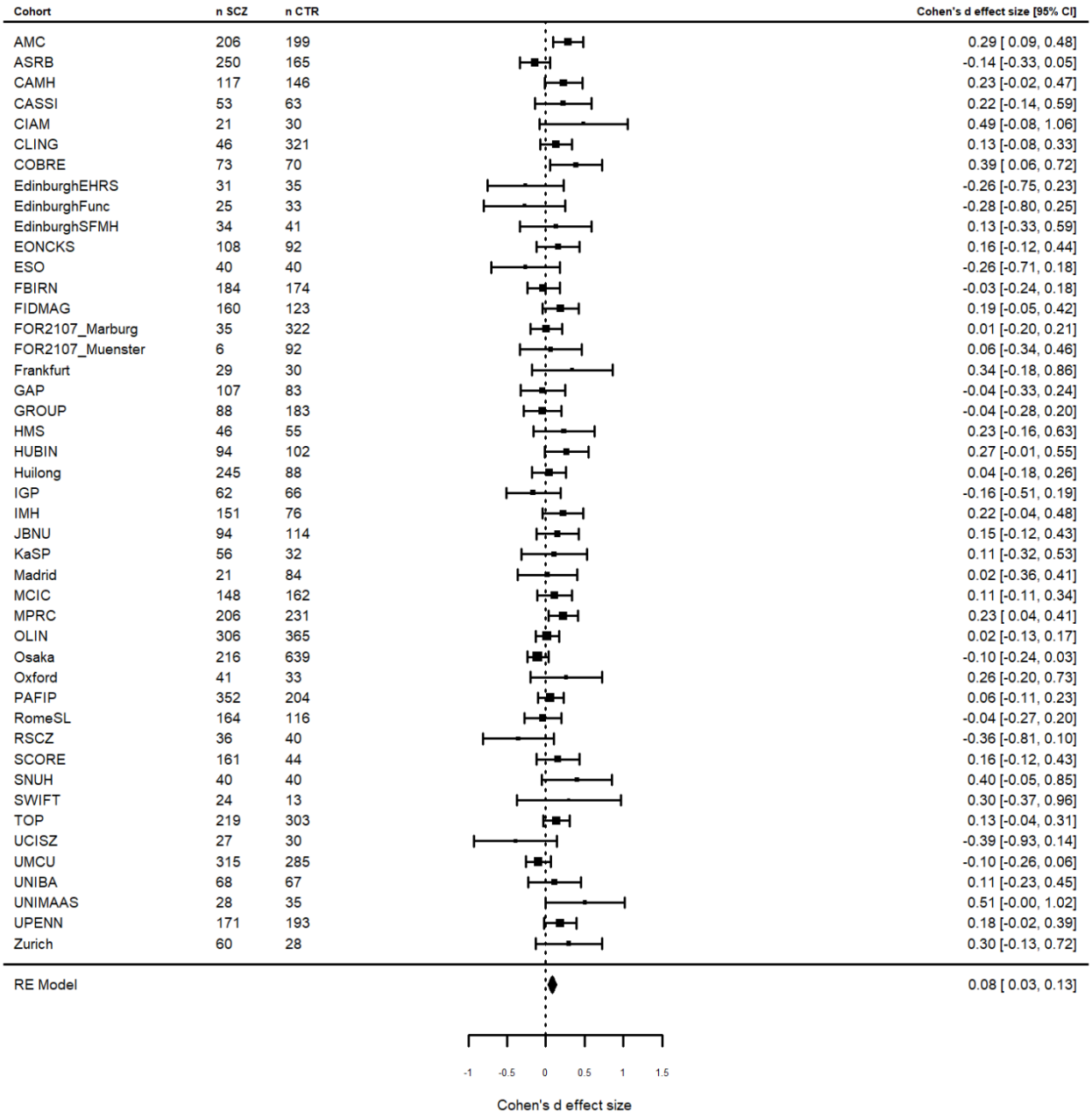
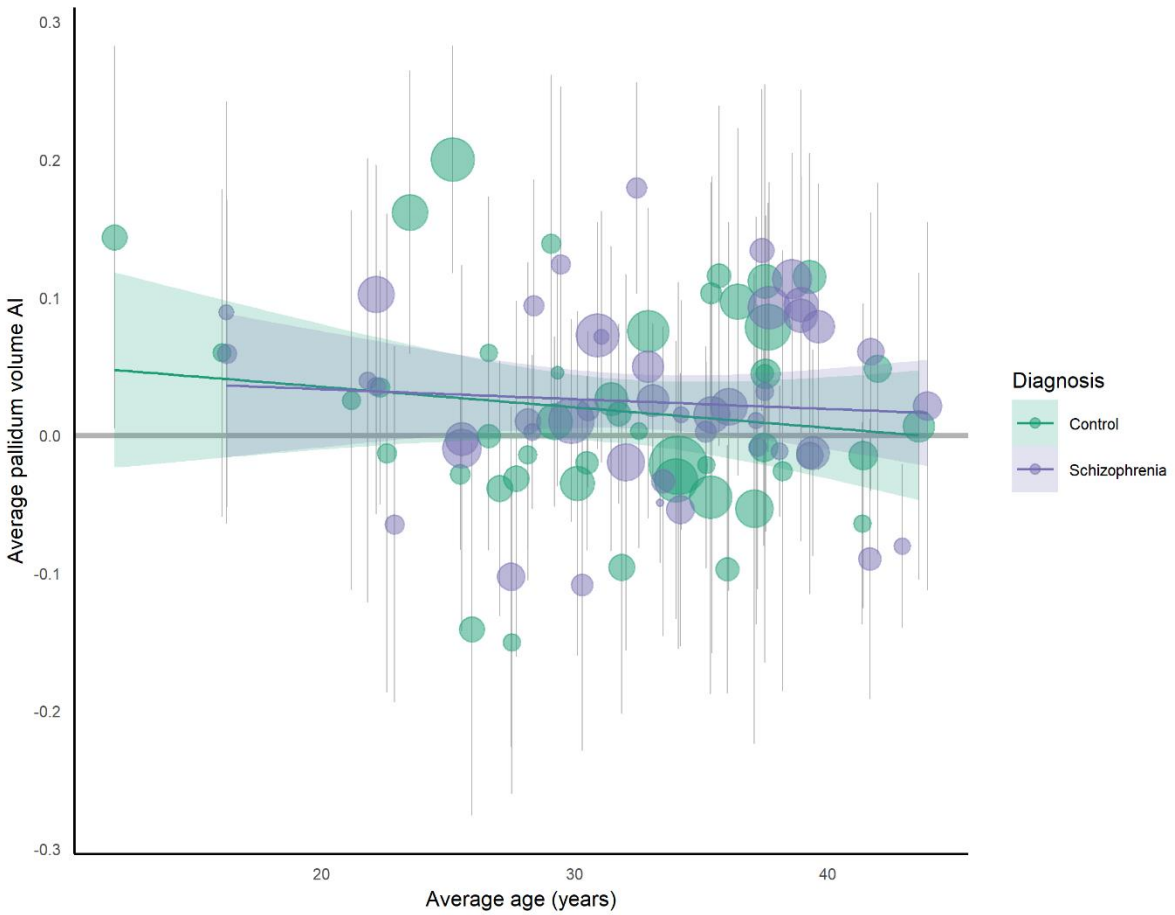


Figure S9. Forest plot for random effects meta-analysis of pallidum volume asymmetry differences between schizophrenia individuals and unaffected controls with age interaction. Per-dataset effect sizes, including confidence intervals, and sample sizes (n SCZ: number of schizophrenia individuals; n CTR: number of unaffected controls) are shown. The sizes of the dots represent the relative dataset sample sizes. The diamond shows the meta-analyzed effect.



Supplementary Figure S10. Average pallidum volume asymmetry against average age per dataset. The average pallidum volume asymmetry index is plotted separately per dataset and for controls (green) and individuals with schizophrenia (purple). Point size indicates the relative sample size of each group per dataset, error bars show standard deviations of the average AI. The regression lines and their shaded confidence intervals show the linear relationships between pallidum volume AIs and age separately in cases and controls – revealing a possible, small diagnosis-by-age interaction effect.

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