Investigating genetic factors driving brain morphology through Neuroimaging studies

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APNS
Applied Physics
for Neuroscience

Outline

Context

Why Imaging Genetics ?

Genetics factors driving brain morphology

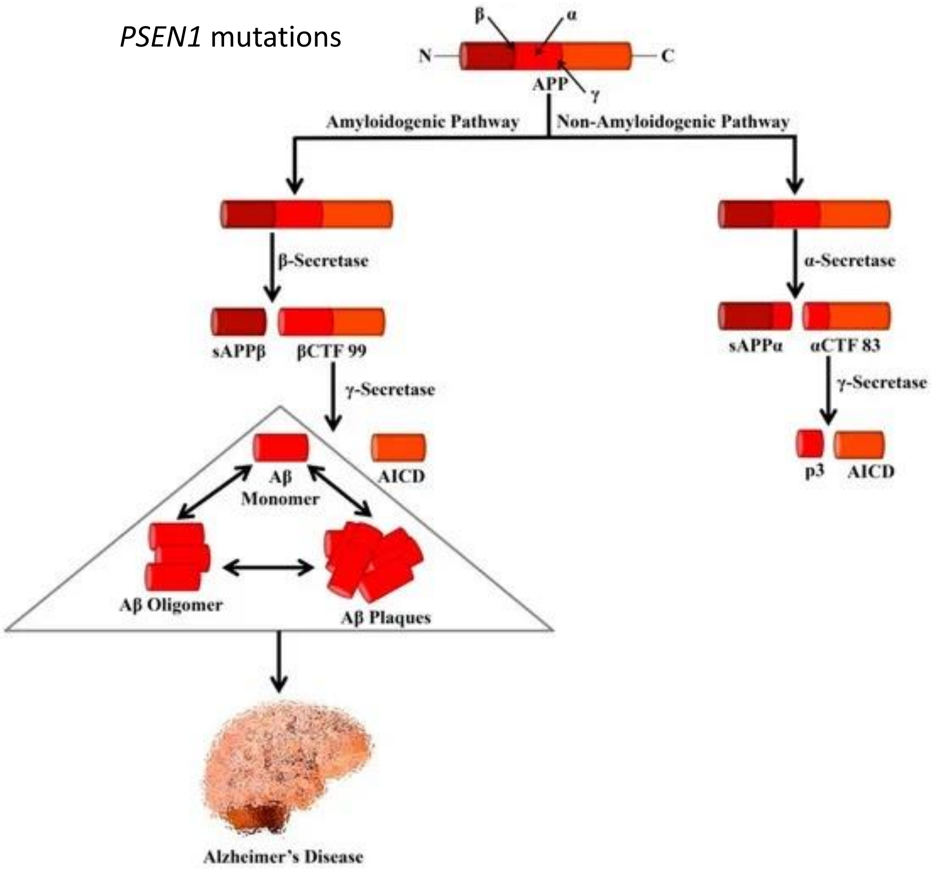
- The genetic architecture of the human cerebral cortex
- Sulcal-based morphometry
- Brain folding heritability
- The genetic architecture of brain folding

Why Imaging **Genetics**?

Genetics:

- Understand biological mechanisms

Amyloid Cascade Hypothesis



PSEN1 mutations

Md. Sahab Uddin, *Int. J. Mol. Sci.* **2020**, *21*(16), 5858; **https://doi.org/10.3390/ijms21165858**

Why Imaging **Genetics**?

Genetics:

- Understand biological mechanisms
- Treatments

Treatments may not work in people with certain genetic variants in a given gene.

Why Imaging **Genetics**?

Genetics:

- Understand biological mechanisms
- Treatments
- Assess individual risk

Knowing risk for disease may change lifestyle habits and medical decisions.

Why **Imaging** Genetics?

Imaging

- Complex Diseases

Diseases or disorders most likely caused by a largely unknown combination of multiple genetic, environmental, and lifestyle factors.

E.g.:

- Alzheimer’s disease
- Autism
- Schizophrenia
- Bipolar Disorder
- & more

Why **Imaging** Genetics?

Imaging

- Complex Diseases

Issues:

- The disease may have a latent period.
- They ignore effects that are stage-specific.
- The disease may be difficult to diagnose.

Why **Imaging** Genetics?

Imaging

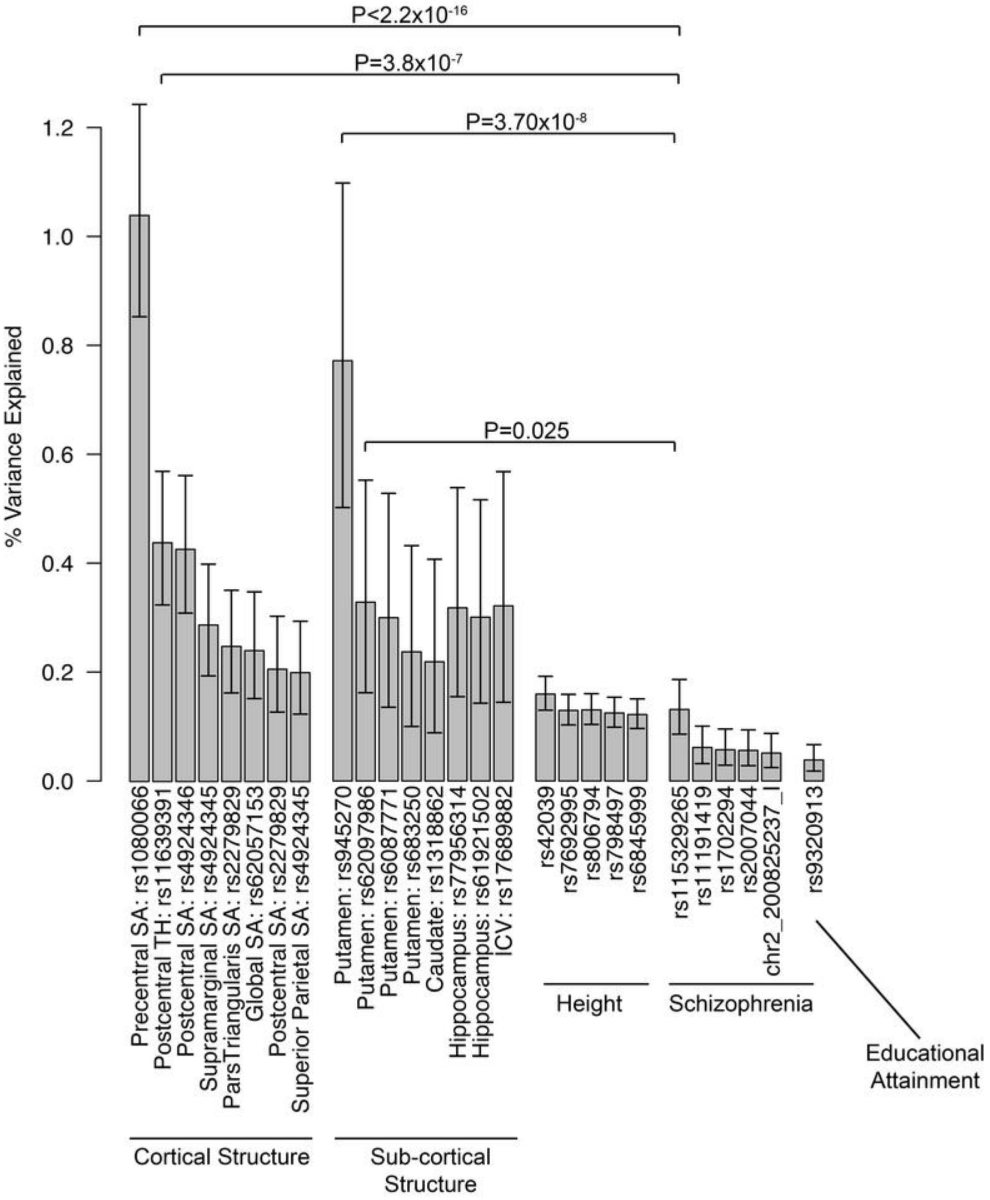
- Complex Diseases

Imaging Genetics

- We can investigate vulnerabilities to disease and stage-specific effects.
- Genetics may be more closely related to brain measures than to disease diagnosis.

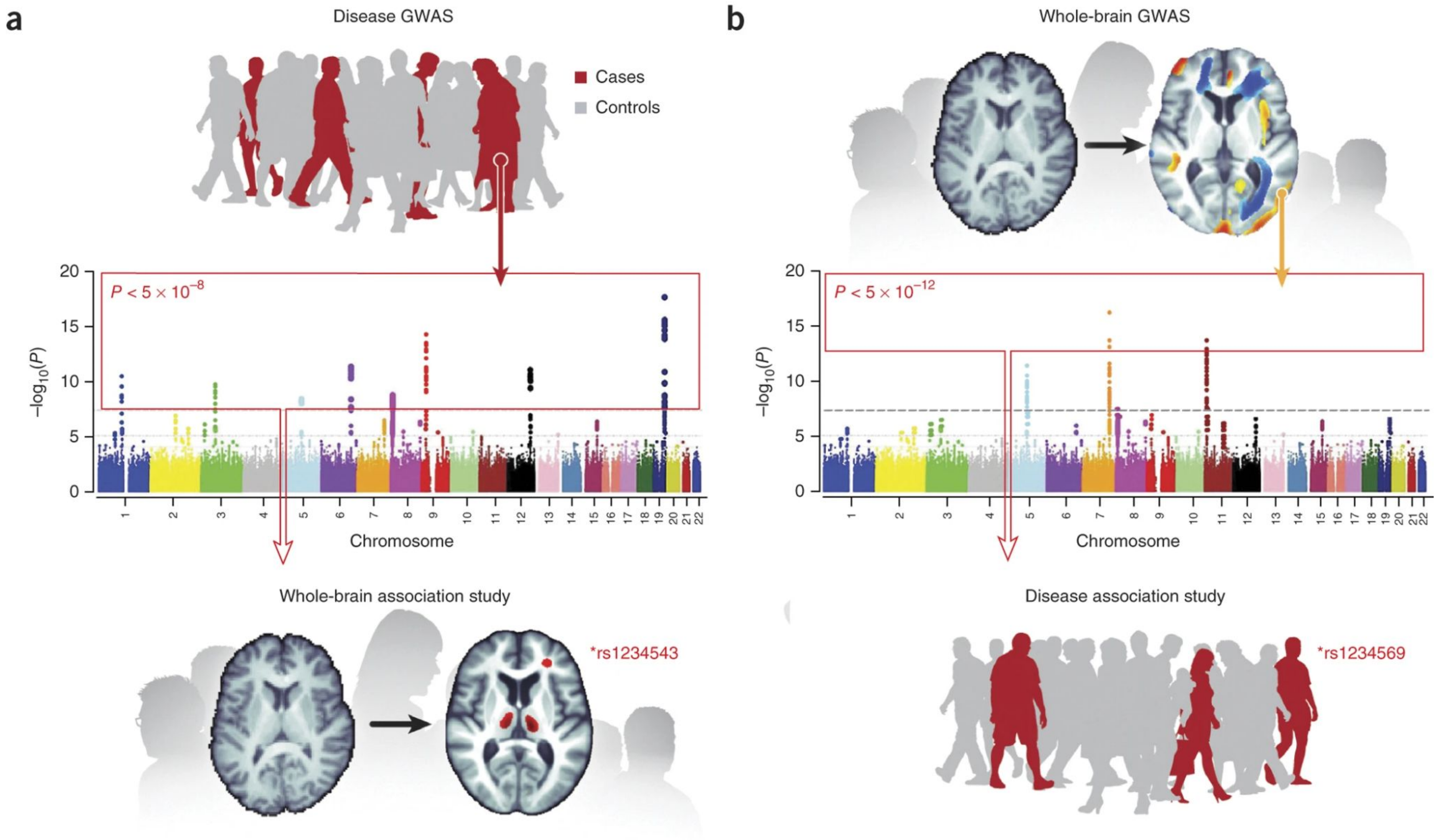
Imaging Genetics

The idea behind imaging genetics is that "genetic variation has a stronger impact on brain traits than on heterogeneous and behaviorally defined disease categories, and that genetic variation associated with brain changes will allow a greater understanding of the mechanism leading to risk for behaviorally defined disorders" **(Le and Stein 2019)**.



Le and Stein, Psychiatry Clin Neurosci, 2019 Jul;73(7):357-369. doi: 10.1111/pcn.12839. Epub 2019 May 21.

Imaging Genetics study designs



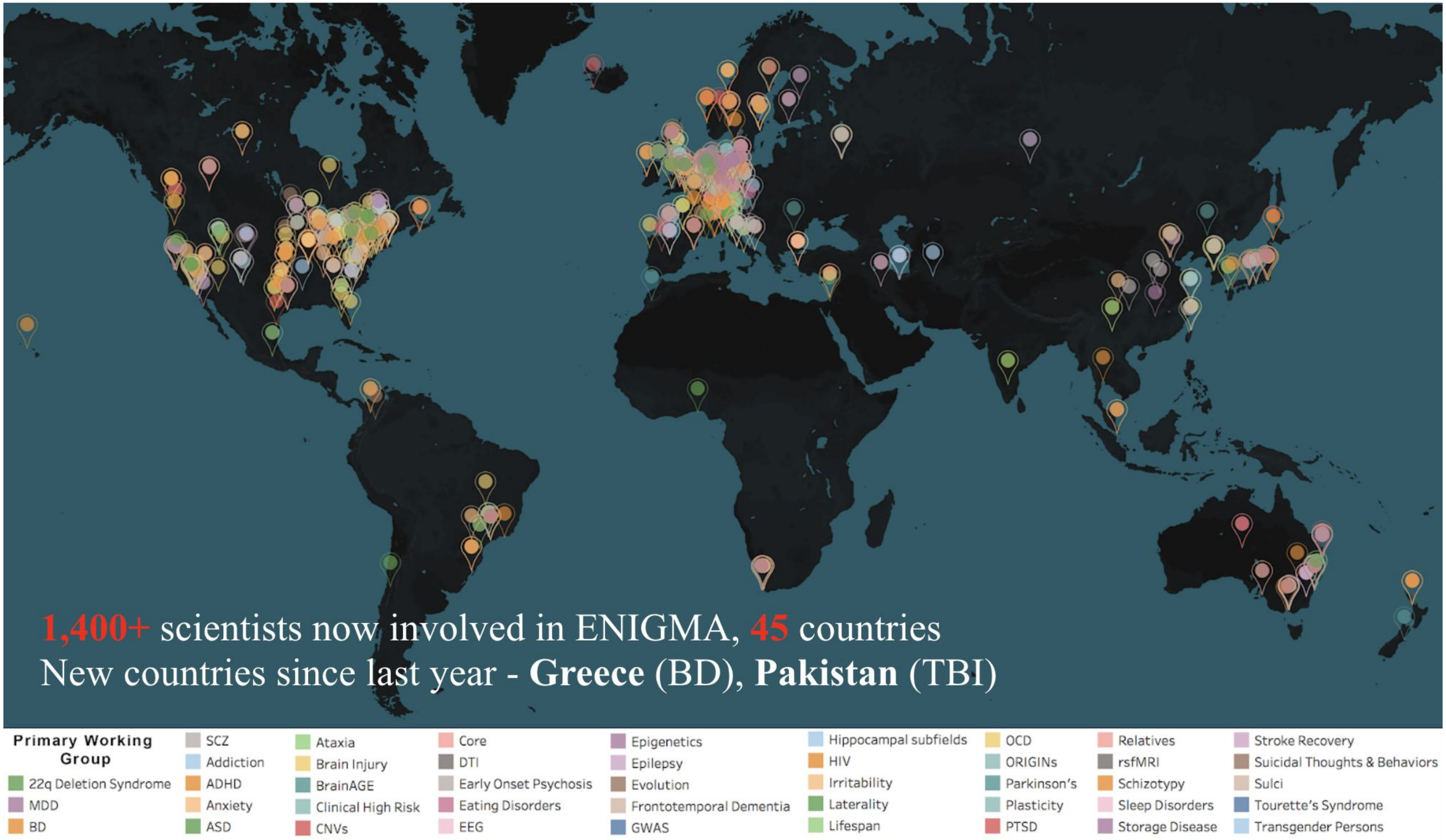
Medland et al., Nature 2014

Imaging Genetics study designs

Need for large N!

- **UK Biobank** (Elliott et al., 2018)
- **CHARGE** (Cohorts for Heart and Aging Research in Genomic Epidemiology) (Bis et al., 2012)
- **ENIGMA** (Enhancing Neuroimaging Genetics through Meta-Analysis) (Thompson et al., 2020)

ENIGMA



1,400+ scientists now involved in ENIGMA, 45 countries

New countries since last year - **Greece** (BD), **Pakistan** (TBI)

https://enigma.ini.usc.edu/

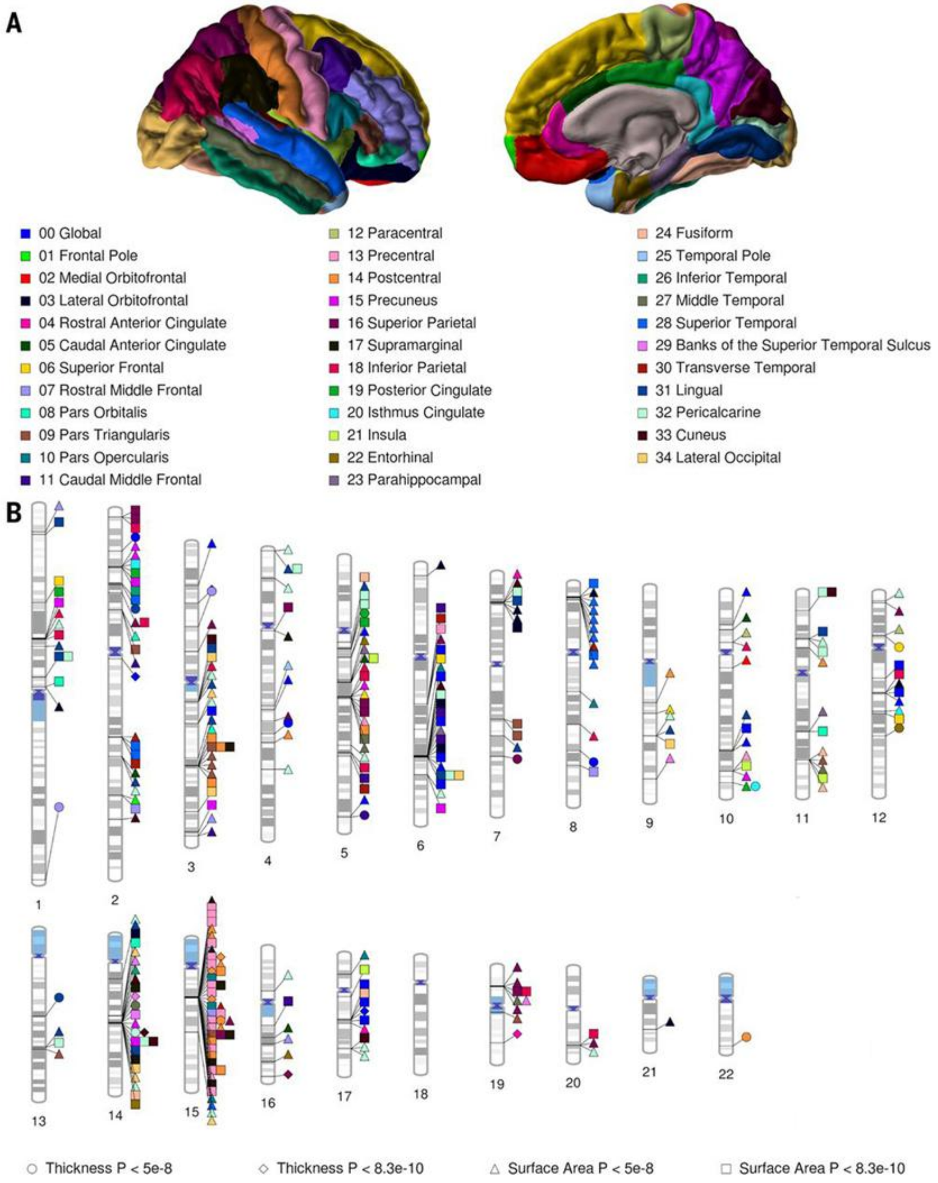
The genetic architecture of the human cerebral cortex

- Genome-wide association meta-analysis

- MRI data from **51,665 individuals** across **60 cohorts**

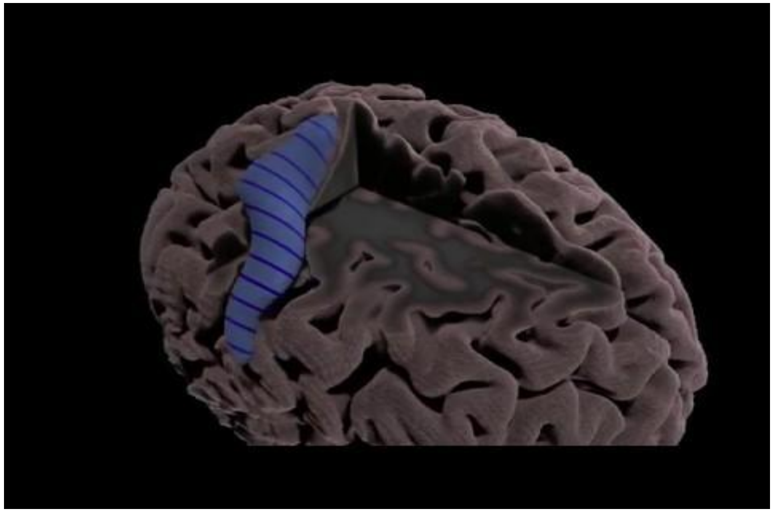
- Surface area and average thickness of the whole cortex and 34 cortical regions with known functional specializations were analyzed

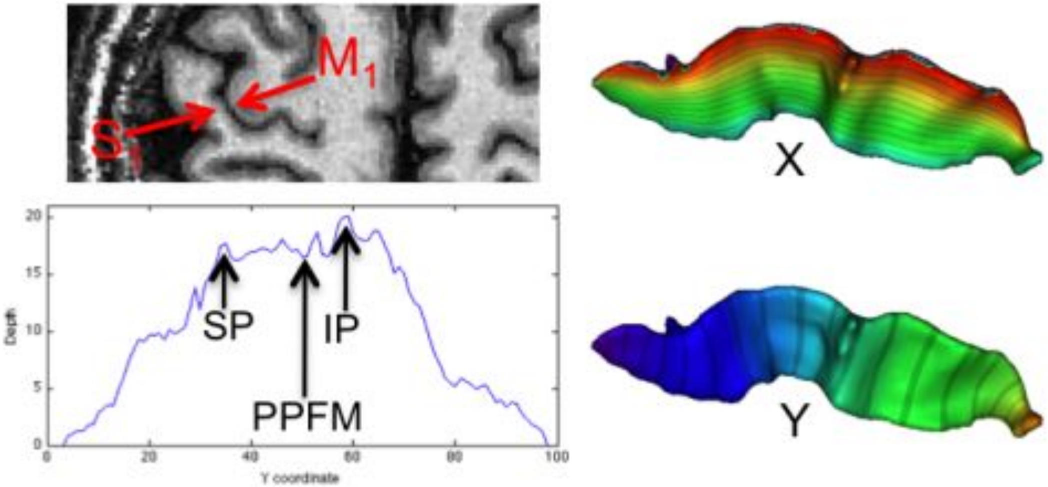
Grasby et al., Science 2020



The genetic architecture of the human cerebral cortex

Central sulcus depth profile





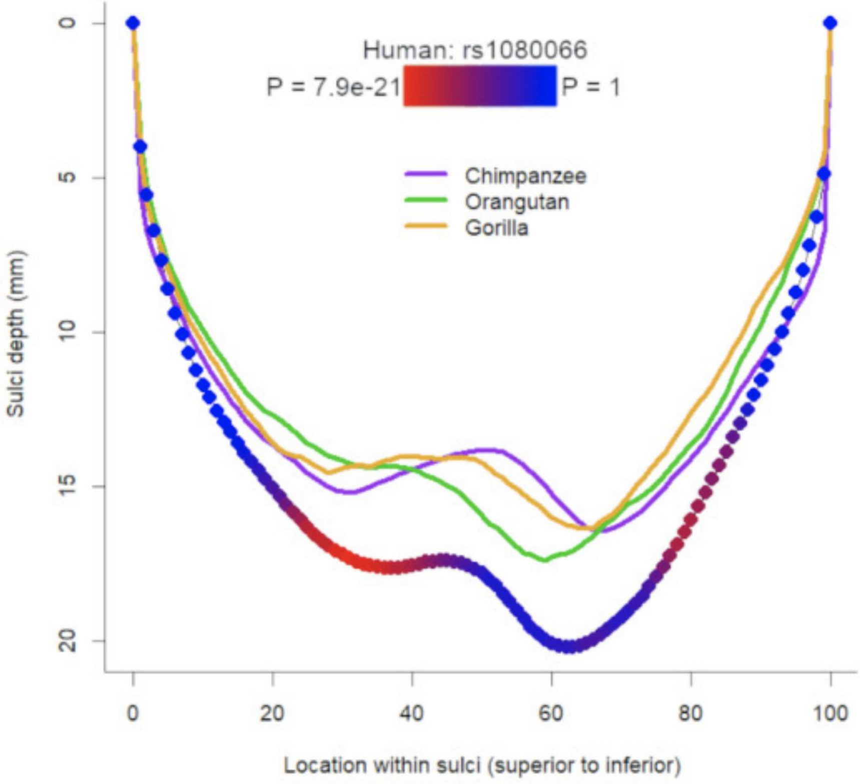
Coulon et al., EMBS 2011

Central sulcus depth profile

○ **N ~ 10,000**

- **Central sulcal depth profile in UK Biobank**

Strongest regional association was observed on chromosome 15q14 with the precentral SA (rs1080066). The maximal association between rs1080066 and sulcal depth was observed around the *pli de passage fronto-pariétal moyen.*



Grasby et al., Science 2020

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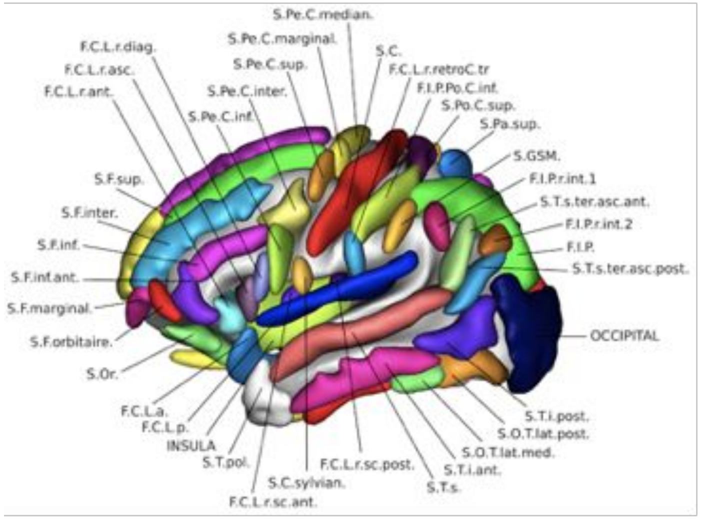
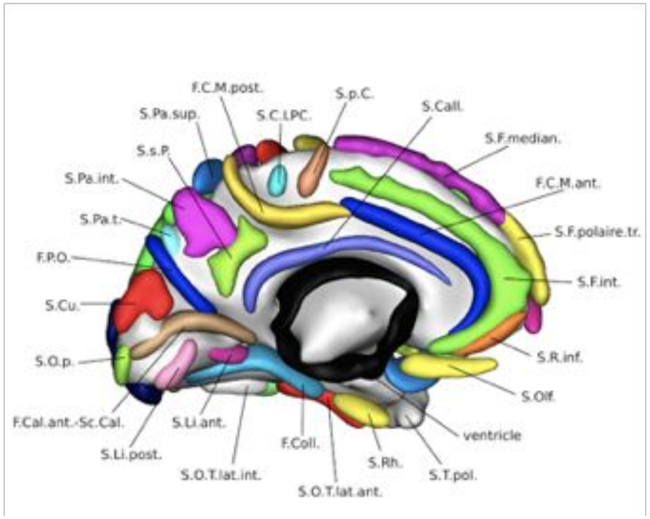
Sulcal-based morphometry

Brain folding





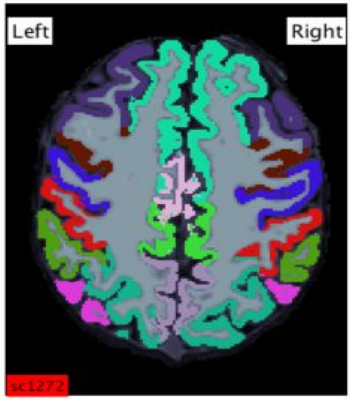
BrainVISA segmentation and labelling

https://brainvisa.info/web/

Perrot et al., Med Image Anal. 2011 Aug;15(4):529-50. doi: 10.1016/j.media.2011.02.008.

Sulci segmentation and labeling protocol

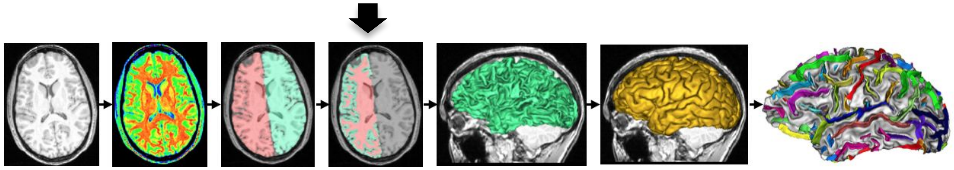
- **1) FreeSurfer**
  Gray/white matter segmentation
  http://freesurfer.net/

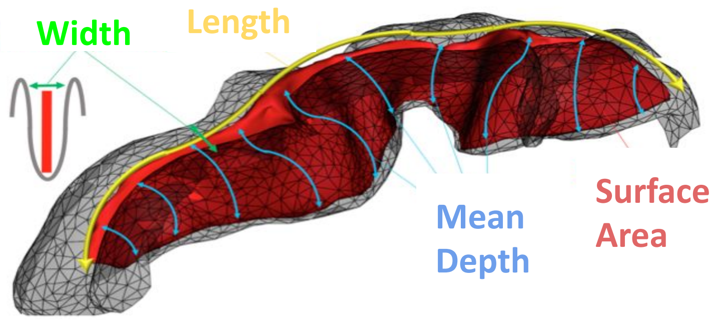


QC-ed FreeSurfer → BrainVISA

- **2) BrainVISA**
  http://brainvisa.info/web/index.html
  From FS gray/white matter surface segments and labels 123 sulci

FreeSurfer Gray/white matter maps

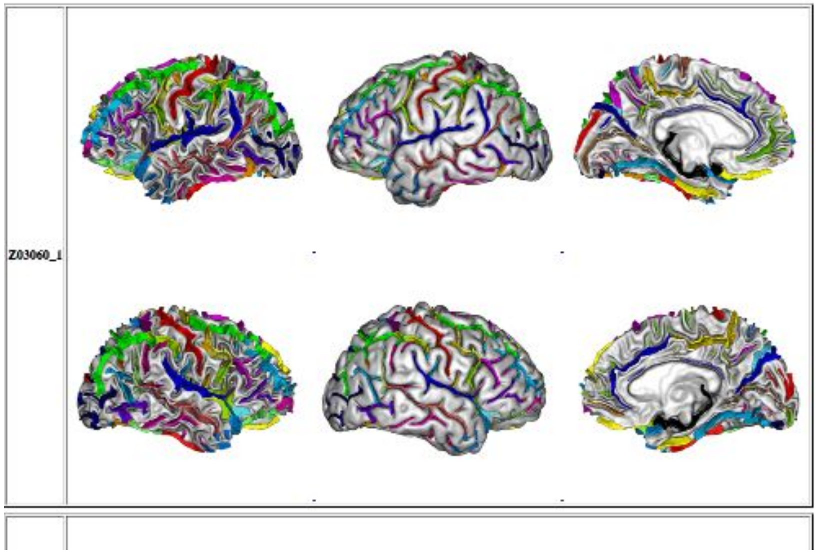




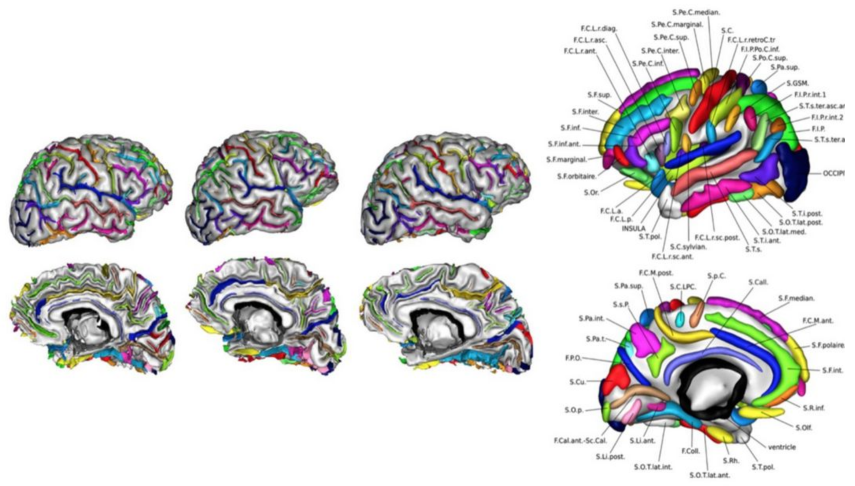
- T1-weighted images
- 123 left/right regions
- Automatic

Sulci segmentation and labeling protocol

Quality Control Webpage



Template



'Reproduced from Perrot, M., Riviere, D., & Mangin, J. F. (2011). Cortical sulci recognition and spatial normalization. Medical Image Analysis, 15(4), 529 - 550.'

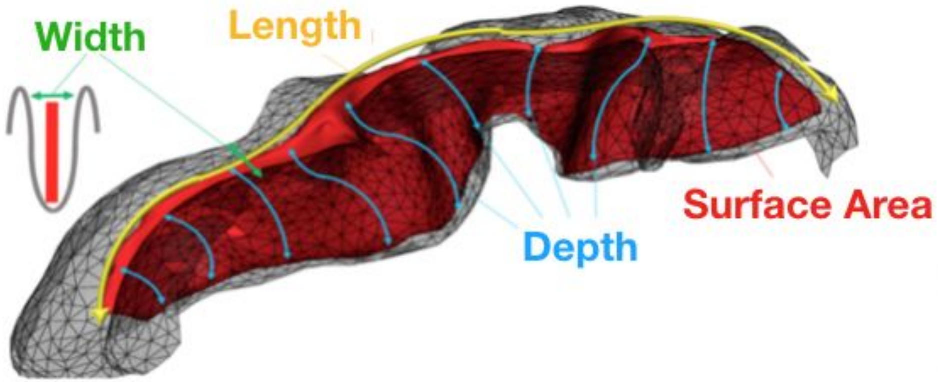
Scroll through subjects with references images for comparison right on the website

Sulci for QC: QC scale

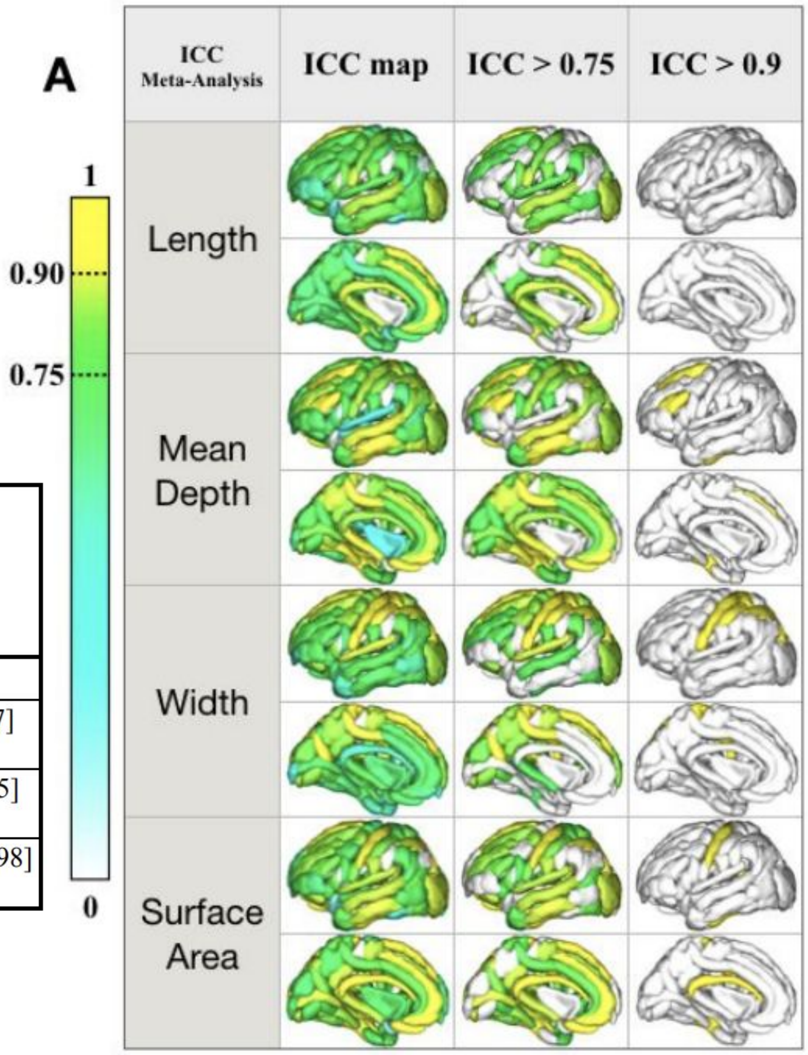
5=solid sulcus piece, no branches, consistent on WM and GM surface
4=solid sulcus piece, allow small branches, consistent on WM and GM surface (4.5 if the calcarine is splitted)
3=main sulcus is well segmented(might not be solid piece), but neighborhood needs correction
2=main sulcus piece has branches, but correct position
1=main sulcus piece has branches, incorrect position

Reliability of sulcal traits

$$\text{ICC} = \frac{\sigma^2_{BS}}{\sigma^2_{BS} + \sigma^2_{WS}}$$



Cohorts	Age Range (mean)	Nº subject (%F)	Inter-scan Interval (days)	Field Strength [T]	Voxel size $[\text{mm}]^3$
KKI	22 – 61 (31.8)	21 (48%)	14	3	[1 x 1 x 1.2]
HCP	24 - 35 (30.1)	35 (44%)	90	3	[0.7 x 0.7 x 0.7]
OASIS	19 - 34 (23.3)	20 (60%)	90	1.5	[1.0 x 1.0 x1.25]
QTIM	21 – 28 (23.2)	34 (37%)	90	4	[0.94 x 0.98 x0.98]



Pizzagalli et al., 2020

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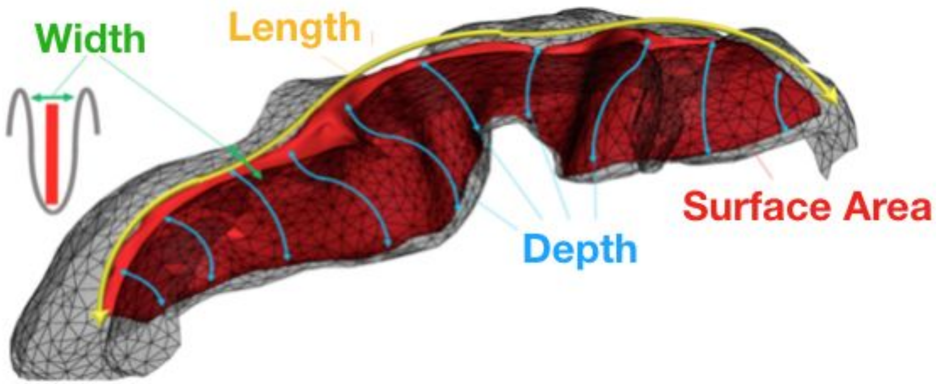
Heritability of sulcal traits



Heritability estimation (narrow-sense)

$$h^2 = \frac{\sigma_g^2}{\sigma_p^2}$$

Additive genetic variance

Phenotypic variance

Left/right genetic correlation

$$\varrho_p = \sqrt{h_L^2}\sqrt{h_R^2} \bullet \varrho_G + \sqrt{1 - h_L^2}\sqrt{1 - h_R^2} \bullet \varrho_E$$

Phenotypic correlation

Genetic correlation

Environmental correlation

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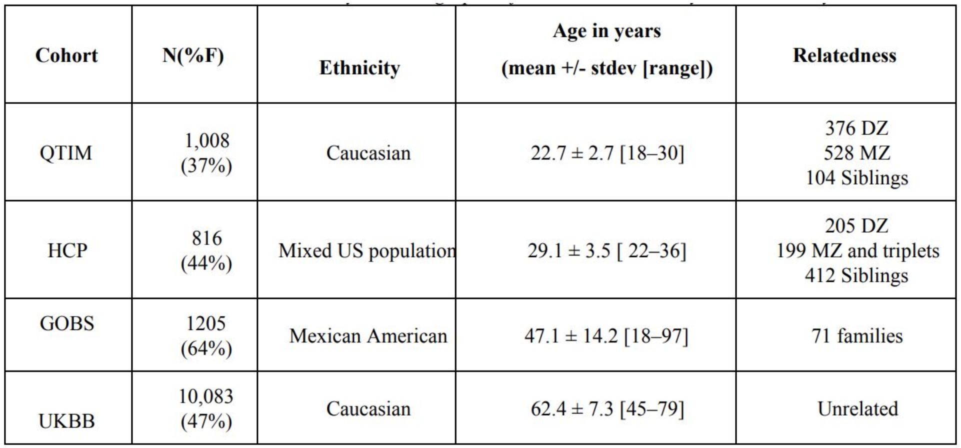
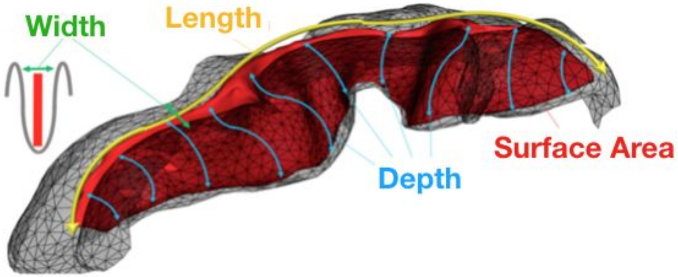
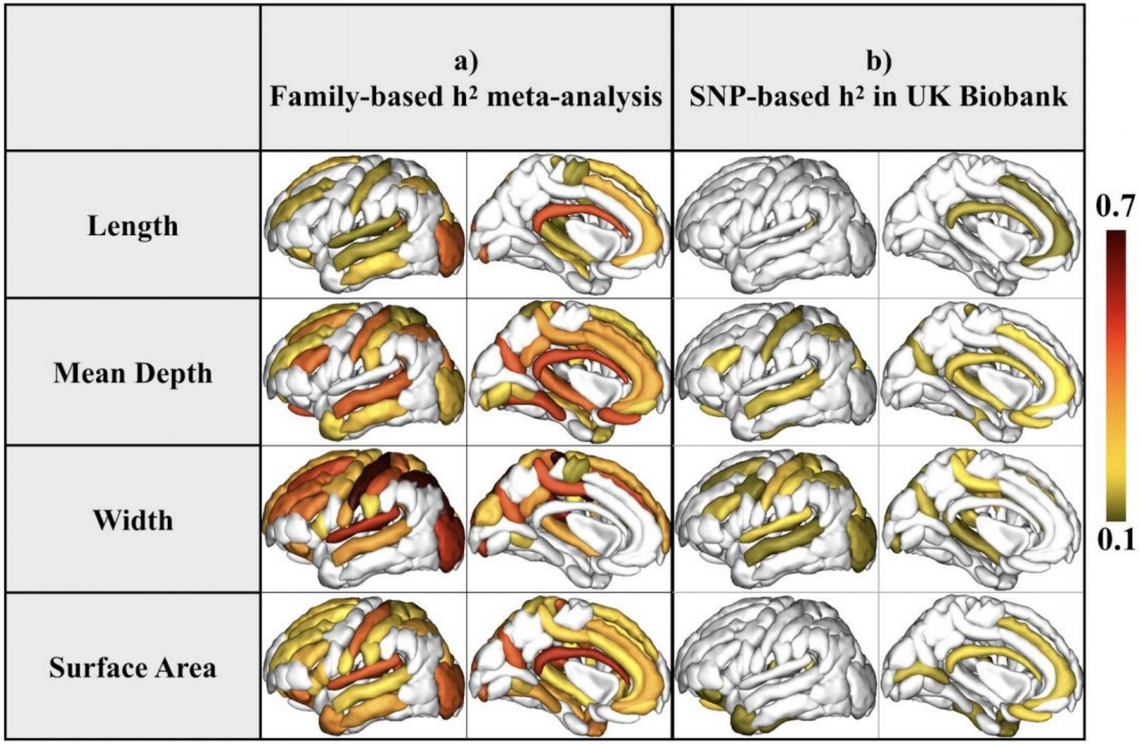
Heritability of sulcal traits

4 independent large cohorts



Cohort	N(%F)	Ethnicity	Age in years (mean +/- stdev [range])	Relatedness
QTIM	1,008 (37%)	Caucasian	22.7 ± 2.7 [18–30]	376 DZ 528 MZ 104 Siblings
HCP	816 (44%)	Mixed US population	29.1 ± 3.5 [22–36]	205 DZ 199 MZ and triplets 412 Siblings
GOBS	1205 (64%)	Mexican American	47.1 ± 14.2 [18–97]	71 families
UKBB	10,083 (47%)	Caucasian	62.4 ± 7.3 [45–79]	Unrelated





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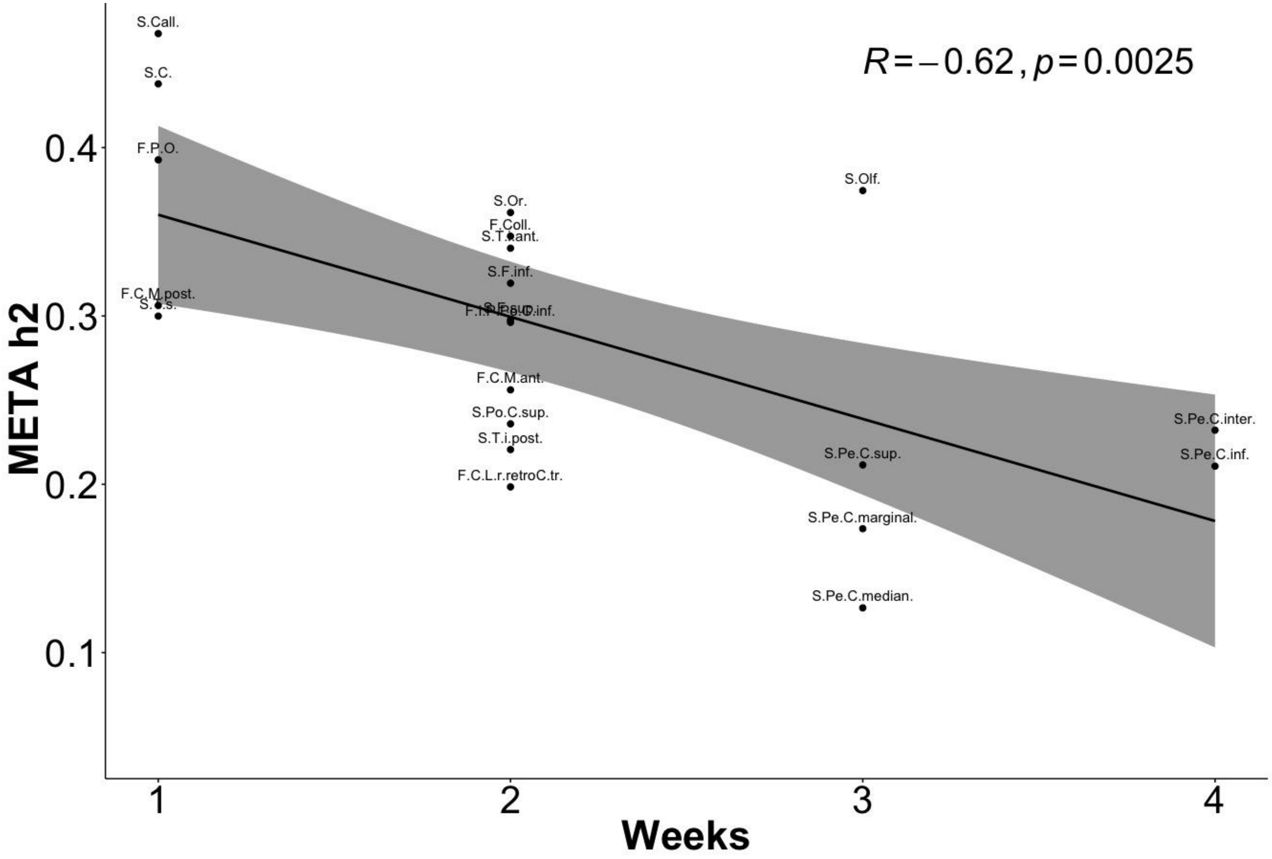
Heritability of sulcal traits



Pearson's correlation between heritability (h^2) and the **appearance of sulci** (in weeks). From Dubois et al. 2018 we grouped the sulci in four groups, 26.7w ("1"), 31.0w ("2"), 34.0w ("3") and 35.7w ("4") [6]. h^2 here has been computed as the average of the heritability of sulca length, mean depth, width and surface area, as estimated by the meta analysis of the bilaterally averages shape measures. The negative correlation (r=-0.62, p=0.0025) suggests that sulci appearing early in brain development are those showing higher estimated heritability.

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$$h^2_{\mathrm{MA-SE}}(S) = \frac{\sum_j se_j^{-2} \times h_j^2(S)}{\sum_j se_j^{-2}}$$

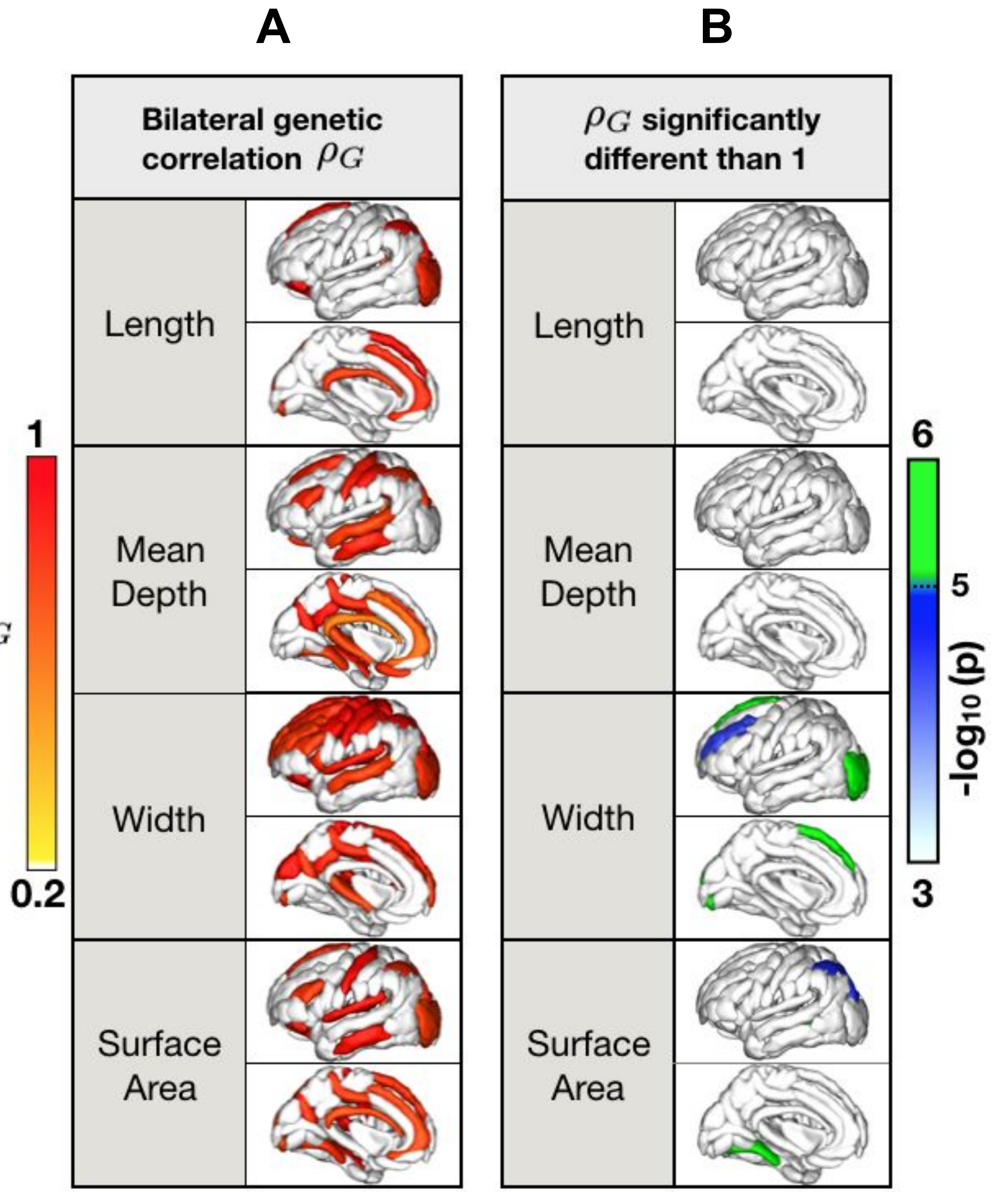
Heritability of sulcal traits

Left/Right genetic correlation

$$\varrho_p = \sqrt{h_L^2}\sqrt{h_R^2} \cdot \varrho_G + \sqrt{1 - h_L^2}\sqrt{1 - h_R^2} \cdot \varrho_E$$

- $\boldsymbol{\rho_G}$ significantly different from zero: a significant proportion of the traits' covariance is influenced by shared genetic factors (**A**).

- Fixing $\boldsymbol{\rho_G = 1}$ we tested for completely genetic overlap (**B**).



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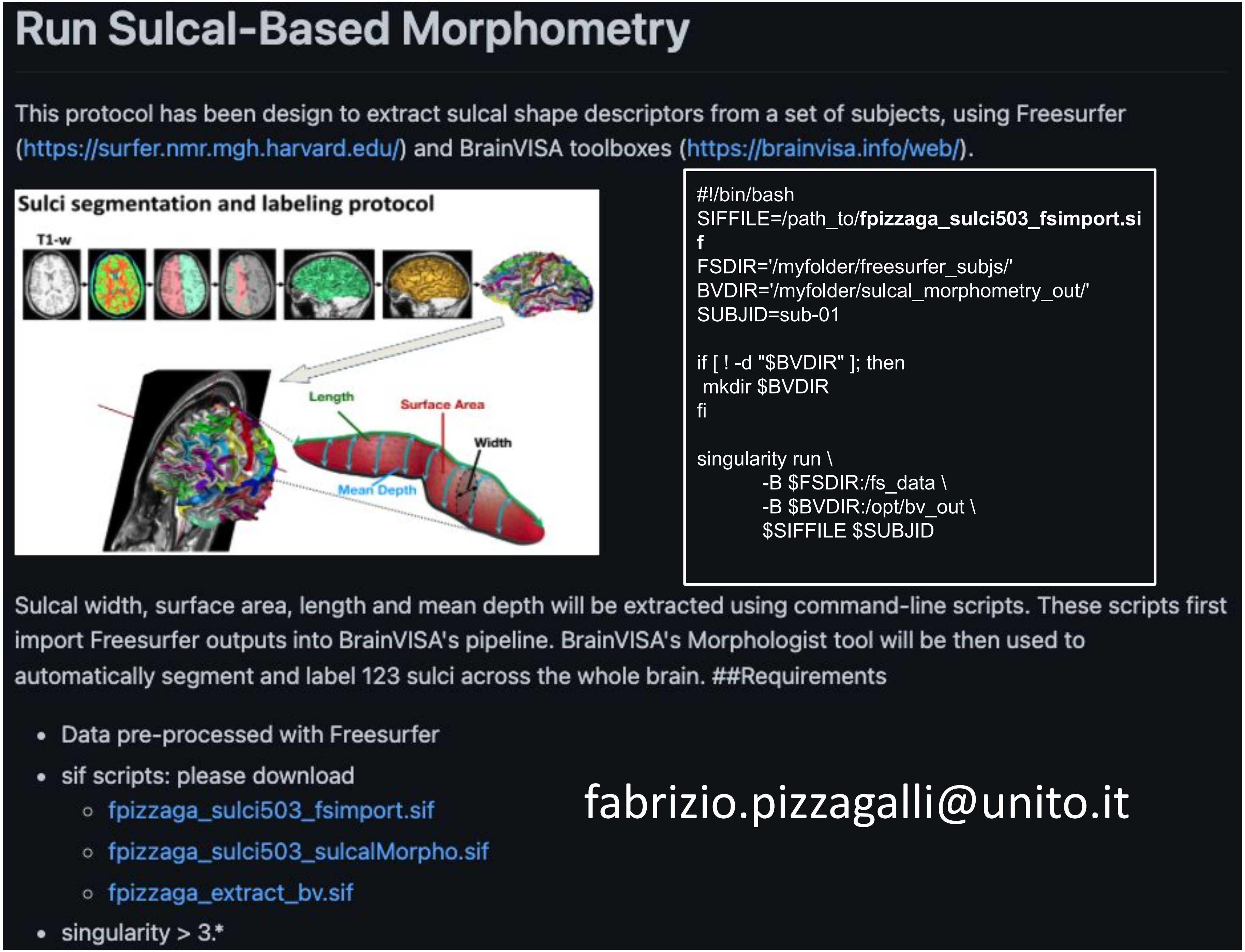

Run Sulcal-Based Morphometry

This protocol has been design to extract sulcal shape descriptors from a set of subjects, using Freesurfer (https://surfer.nmr.mgh.harvard.edu/) and BrainVISA toolboxes (https://brainvisa.info/web/).

```
#!/bin/bash
SIFFILE=/path_to/fpizzaga_sulci503_fsimport.sif
FSDIR='/myfolder/freesurfer_subjs/'
BVDIR='/myfolder/sulcal_morphometry_out/'
SUBJID=sub-01

if [ ! -d "$BVDIR" ]; then
 mkdir $BVDIR
fi

singularity run \
          -B $FSDIR:/fs_data \
          -B $BVDIR:/opt/bv_out \
          $SIFFILE $SUBJID
```

Sulcal width, surface area, length and mean depth will be extracted using command-line scripts. These scripts first import Freesurfer outputs into BrainVISA's pipeline. BrainVISA's Morphologist tool will be then used to automatically segment and label 123 sulci across the whole brain. ##Requirements

- Data pre-processed with Freesurfer
- sif scripts: please download
  - fpizzaga_sulci503_fsimport.sif
  - fpizzaga_sulci503_sulcalMorpho.sif
  - fpizzaga_extract_bv.sif
- singularity > 3.*

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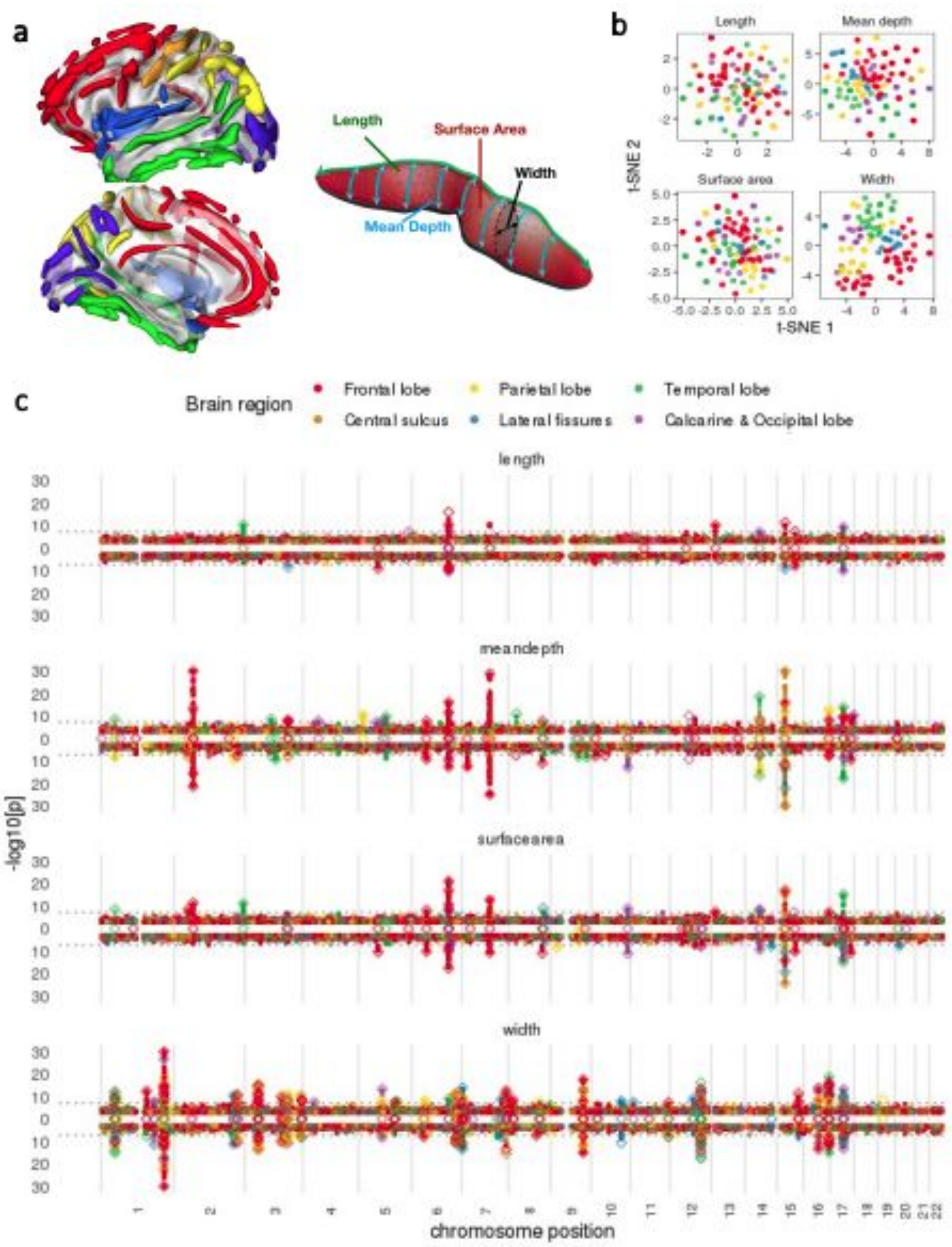
Genetic map of regional sulcal morphology in the human brain



Large-scale genome-wide associations of regional brain cortical sulcal measures derived from MRI data of **40,169 individuals** in the UK Biobank

Sun et al., https://doi.org/10.1101/2021.10.13.463489, biorxiv

Thank you!

Acknowledgments

Caterina Guiot
Federico D'agata
Eleonora Ficiarà
Paolo Provero
Alessandro Vercelli

Neda Jahanshad
Paul Thompson
Sophia Thomopoulos
Elizabeth Haddad
Jessica Turner

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