

Analyzing Brain Taxonomy Trees

Chris Hammill and Jason Lerch

August 31, 2018



Overview

- Use hierarchical modelling in Stan to improve efficiency of brain anatomy studies.
- Focus on mouse brain, but generalizes naturally to other species (humans) and measures (function).

A hypothetical study

- Want to estimate the effect of a drug on brain development
- 10 control mice
- 10 mice receive the drug
- Localize in space where the treated mouse brains differ from controls

Analysis Pipeline

- Automatically label the regions of the brain
- Bring brain images into alignment - **registration**
- Take a labelled brain - **atlas**
- Propagate labels from the atlas to the images
- Compute structure volumes
- Find regions where volumes differ

Traditional Analysis

Massively Univariate Modelling

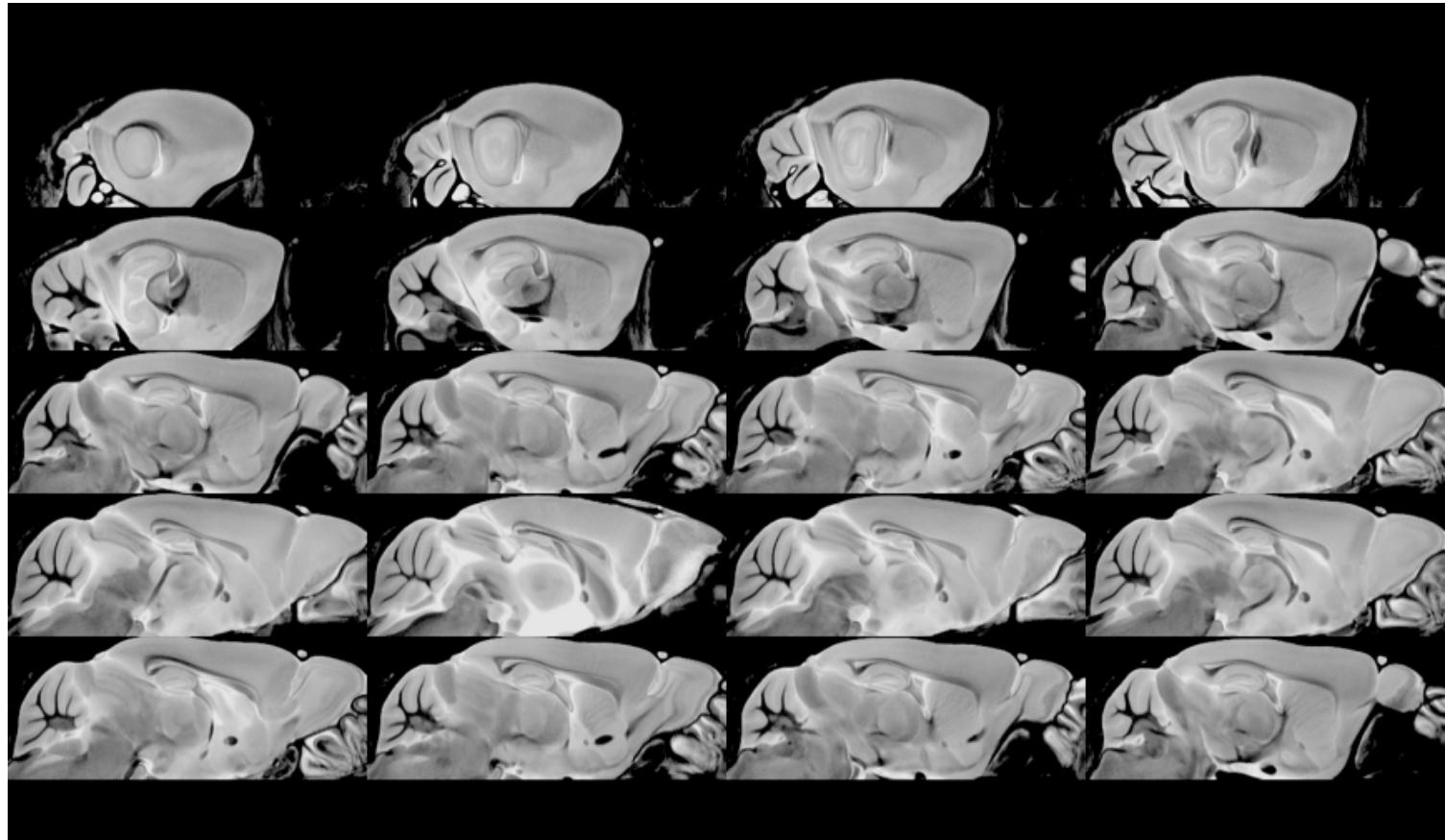
- Fit one linear model per structure
- Extract t-statistics
- Compute p-values
- FDR control

Traditional Analysis

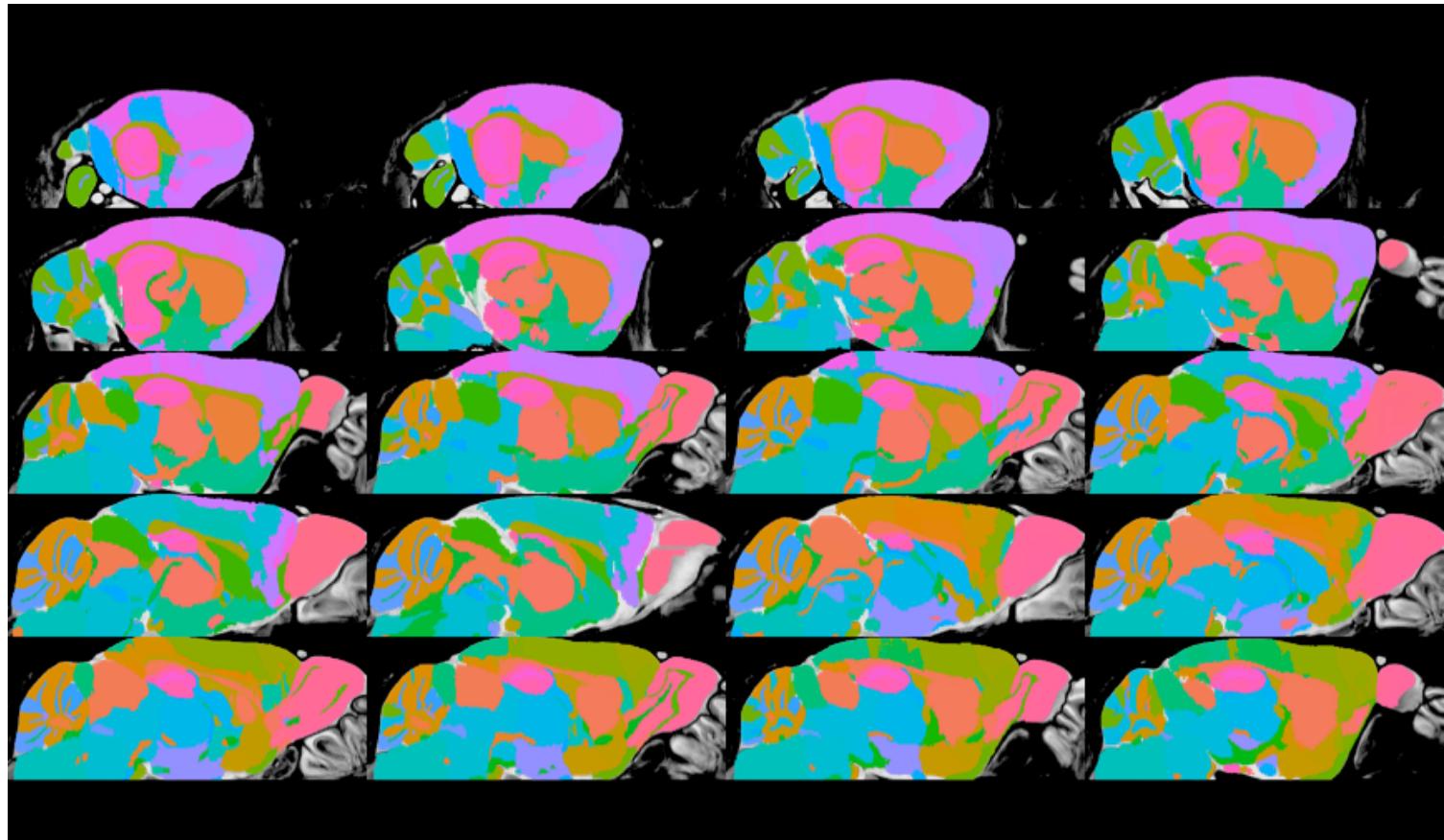
Massively Univariate Modelling

- Fit one linear model per structure
- Extract t-statistics
- Compute p-values
- FDR control
- No pooling

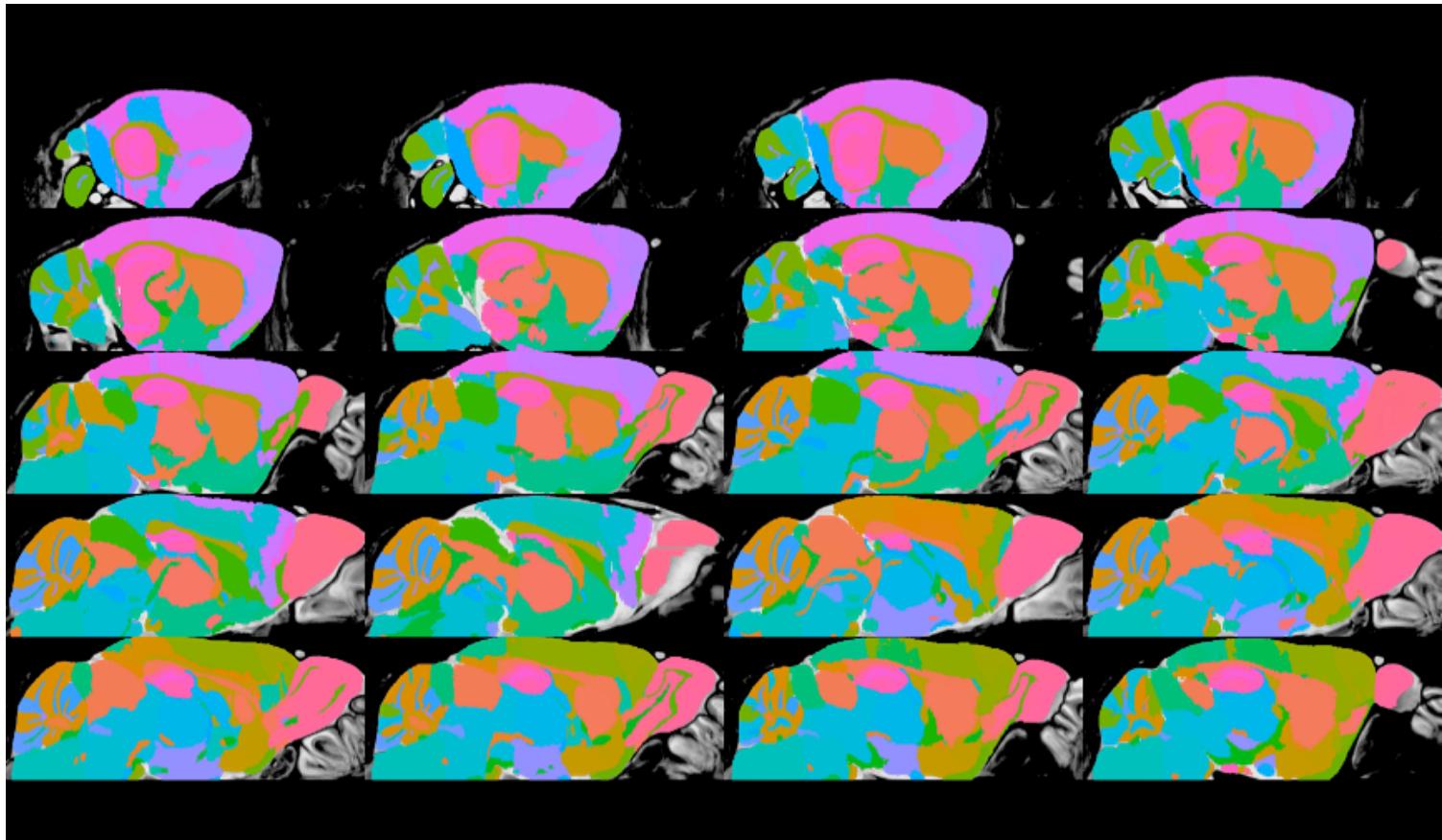
The Mouse Brain



The Mouse Brain Labelled



The Mouse Brain Labelled



- Fit 336 linear models

Downside

- Ignore covariance
- Unable to borrow strength from similar structures
- Needs separate analyses for multiple scales

First Improvement: Allow for pooling

- Use brain structure to construct hierarchical model
- Pool effects of interest across structures
- $y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (1 \mid \text{ID})$

What we gain

- This already has advantages over unpooled models.
- Structures can borrow strength from each other.
- Individual level effects can be estimated

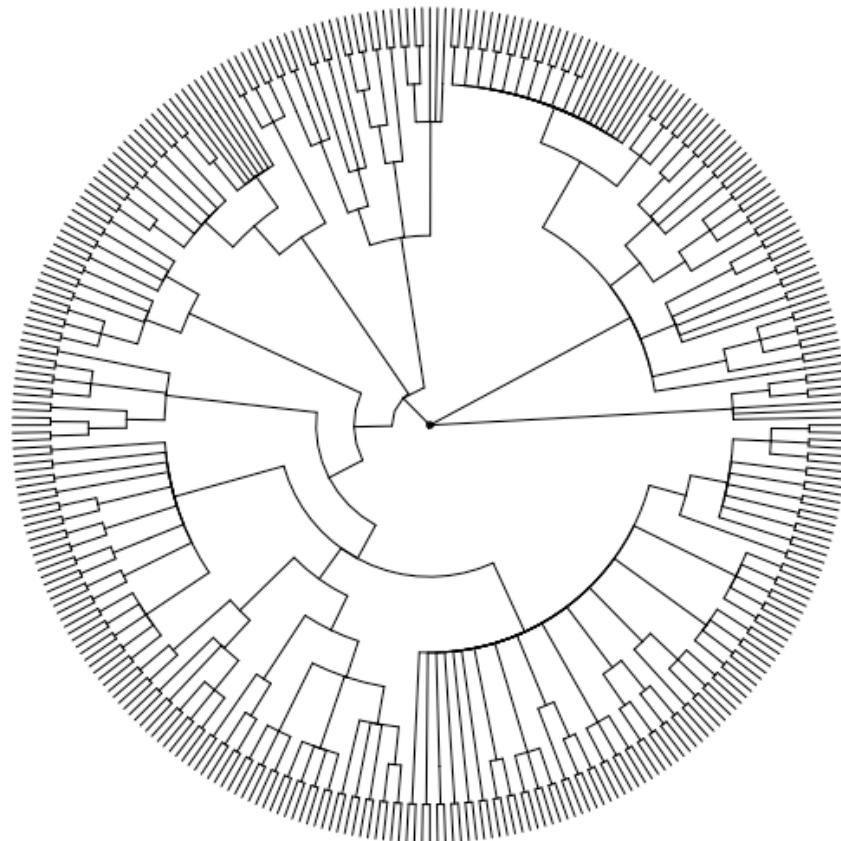
What we gain

- This already has advantages over unpooled models.
- Structures can borrow strength from each other.
- Individual level effects can be estimated

Room for improvement

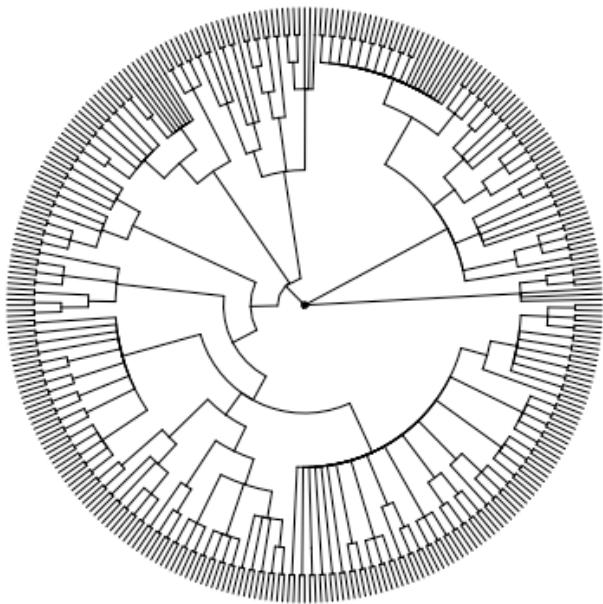
- Pooling is driven only by structure variance
- We are ignoring lots we know about the brain

The Mouse Brain Tree



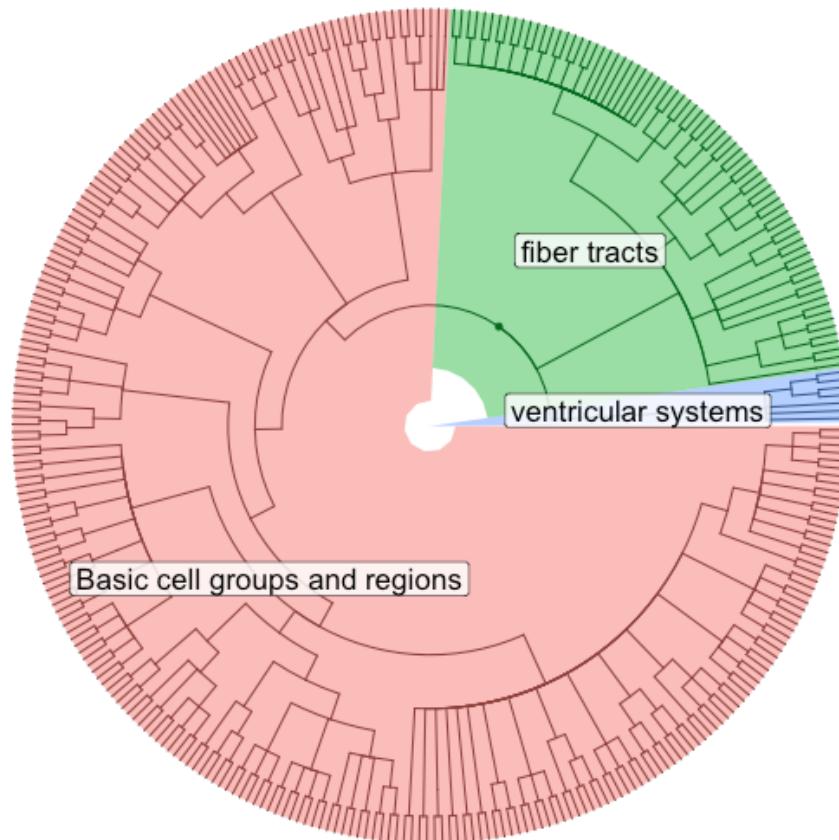
- Hierarchy from histology atlas from the Allen Institute

A tree structured atlas

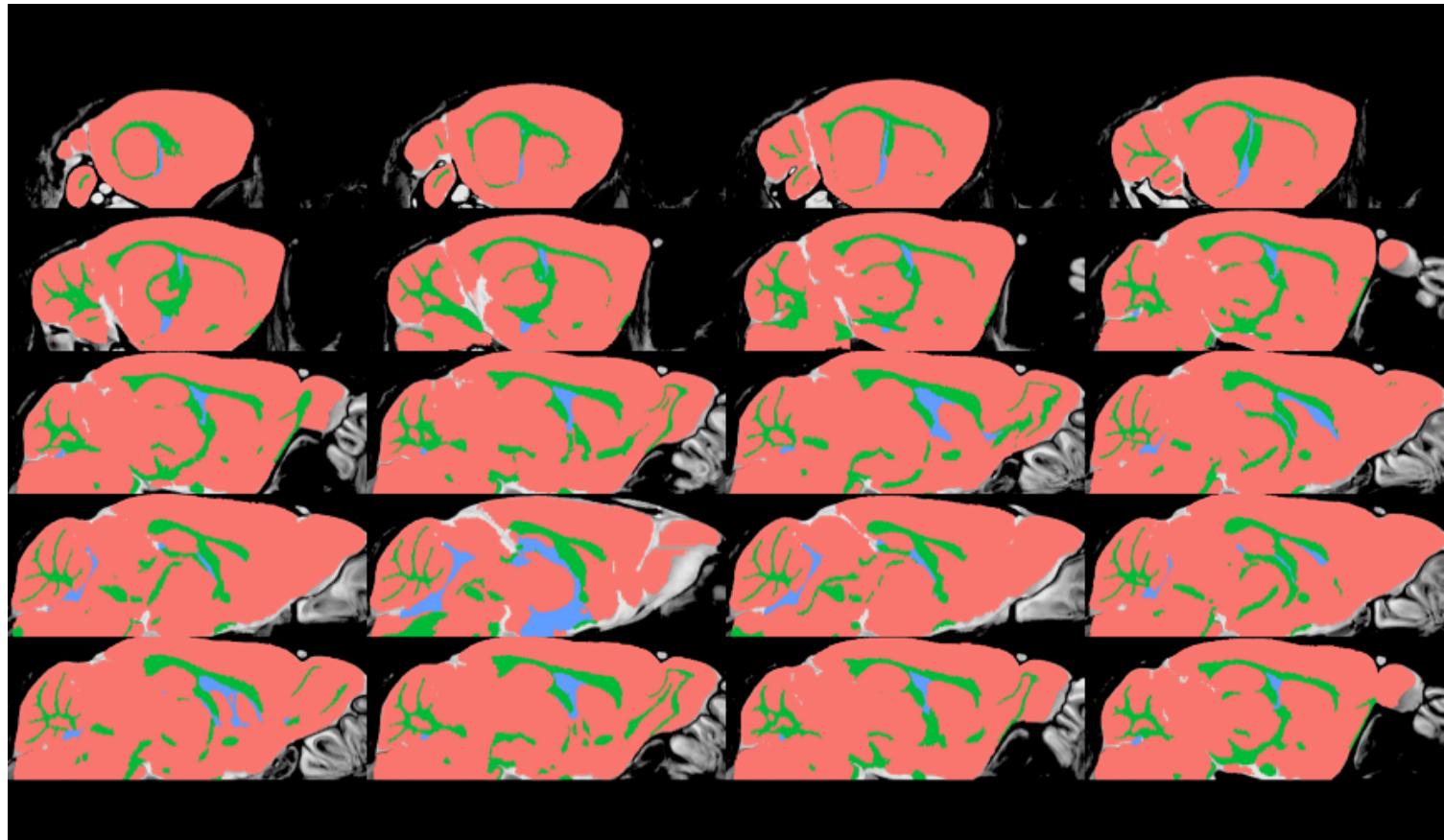


- Hierarchical MRI atlas
- Structures organized into the taxonomy shown before

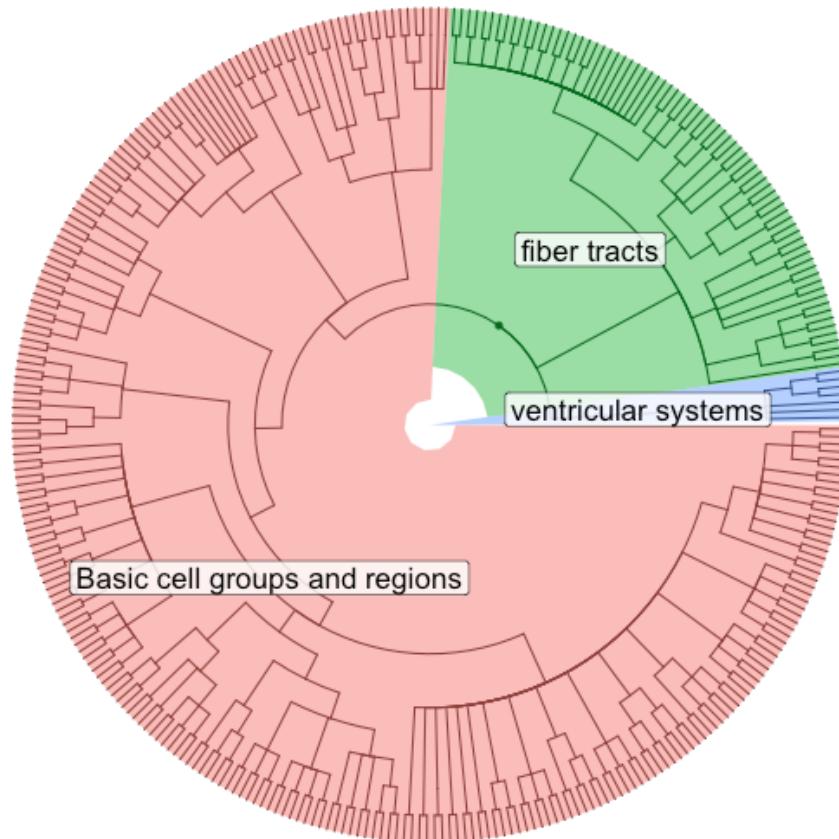
The First Split



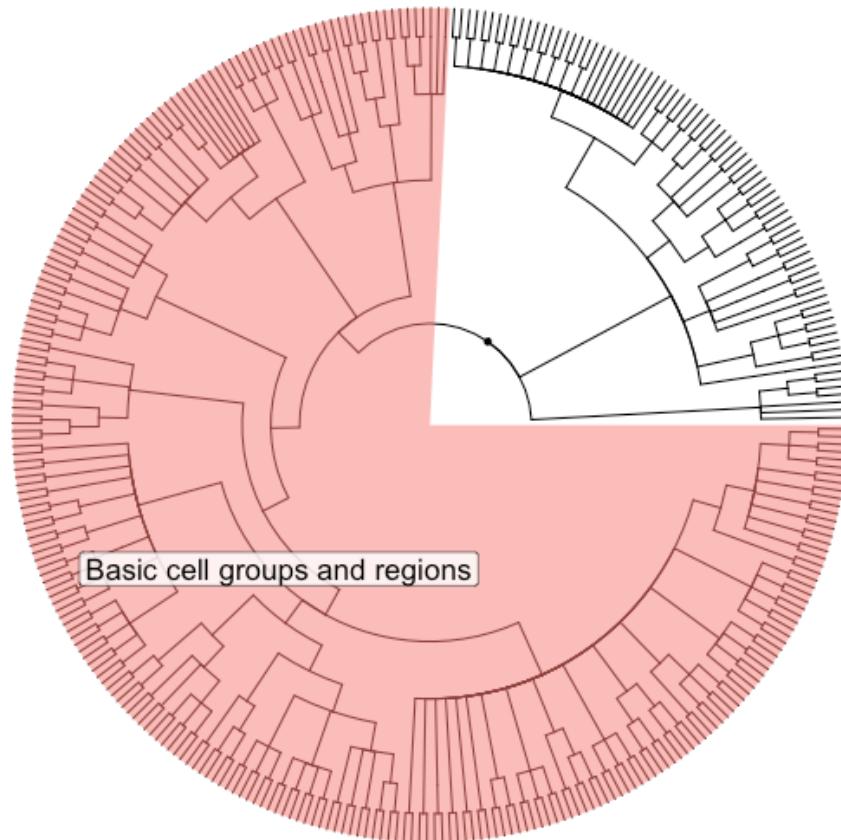
The First Split



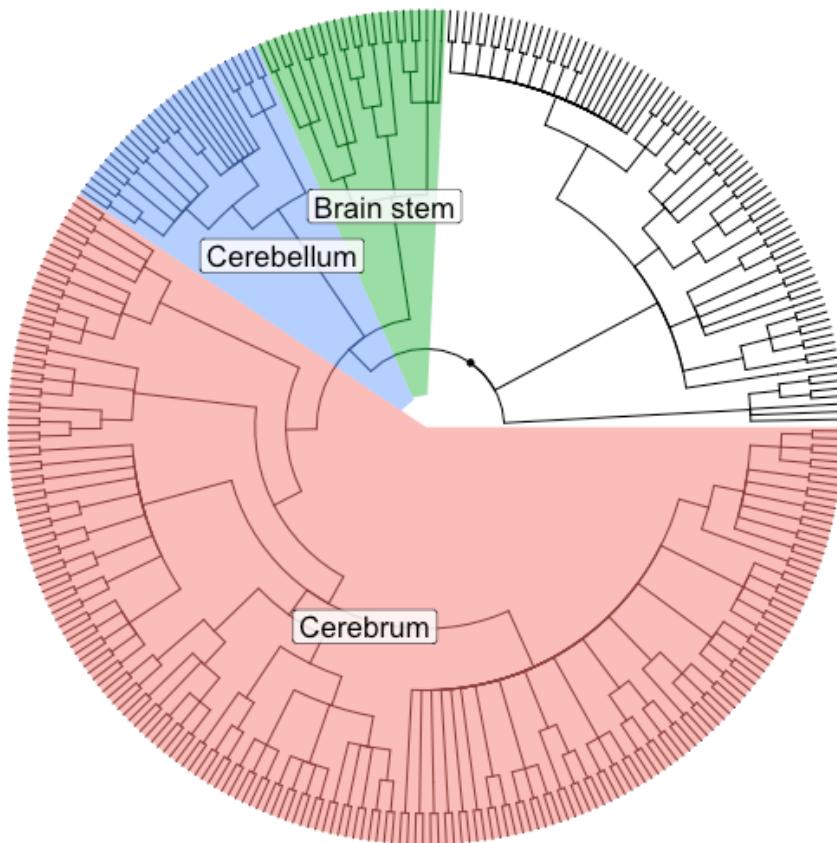
Subdividing the Grey Matter



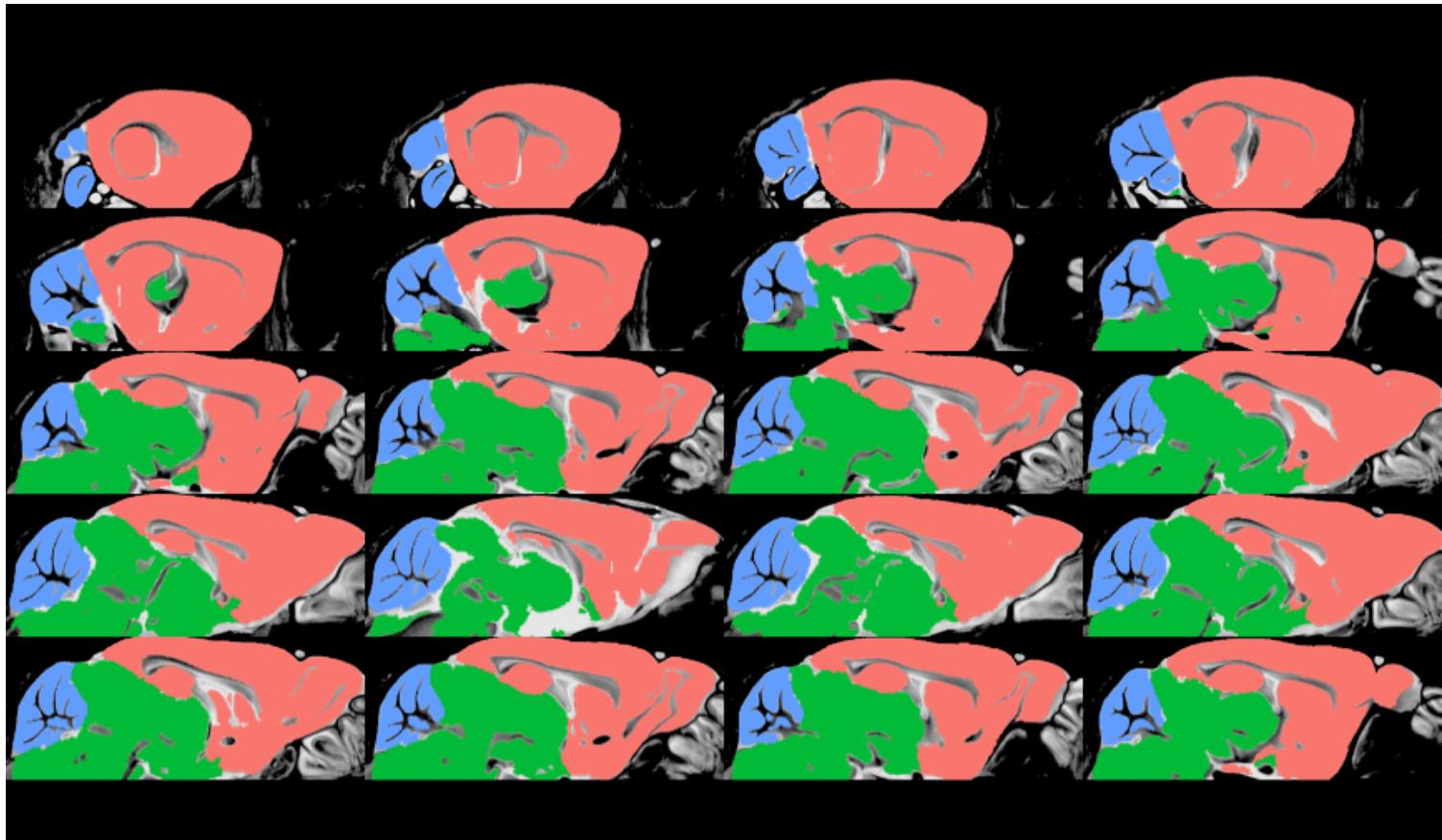
Subdividing the Grey Matter



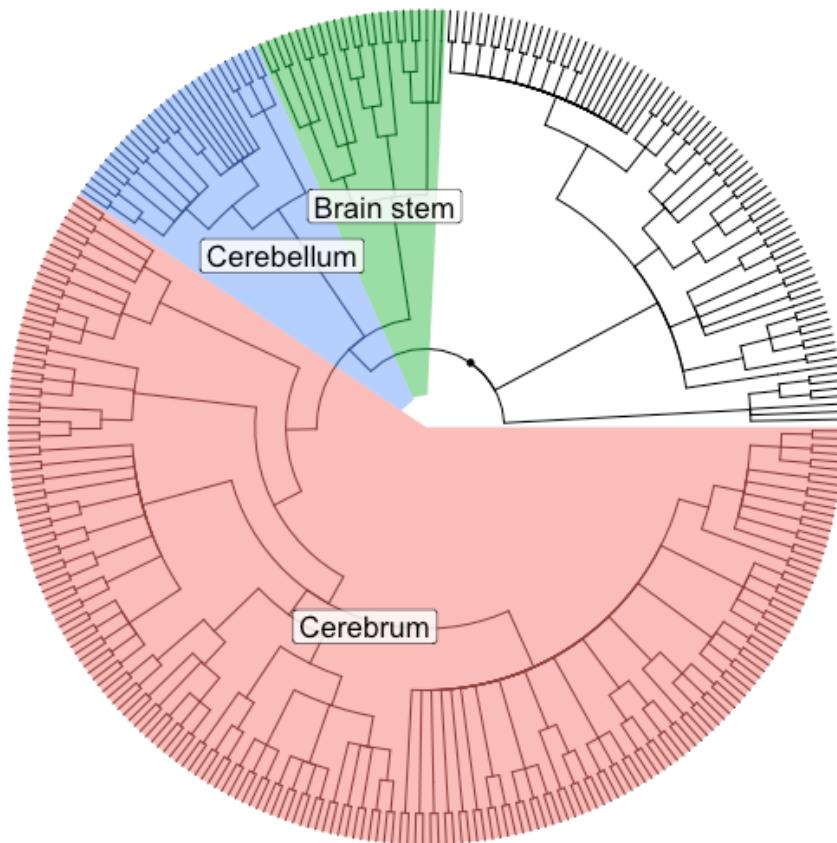
Subdividing the Grey Matter



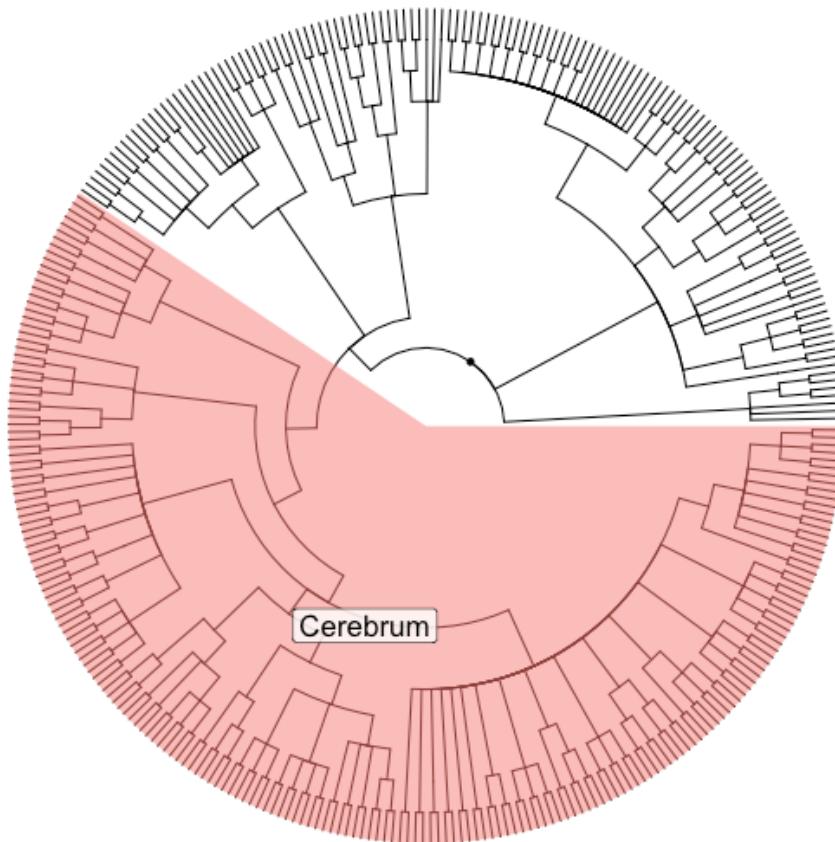
Subdividing the Grey Matter



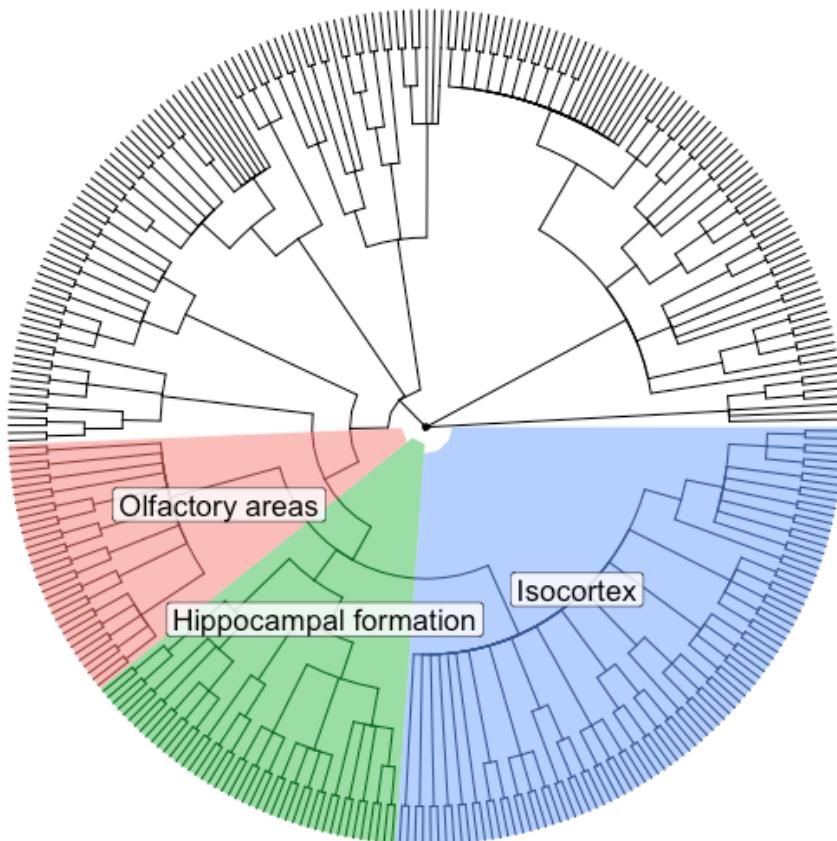
Subdividing the Grey Matter



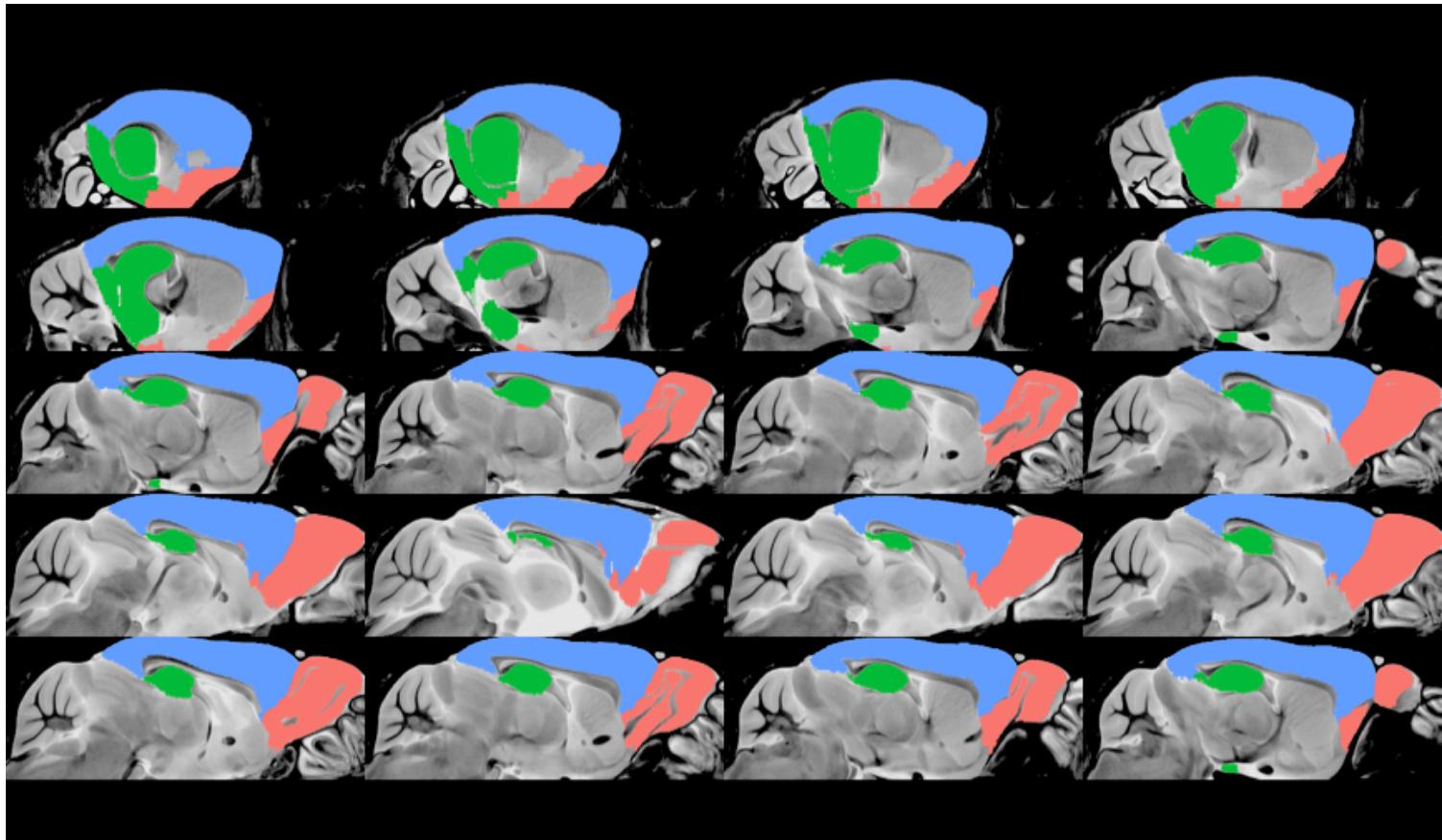
Subdividing the Grey Matter



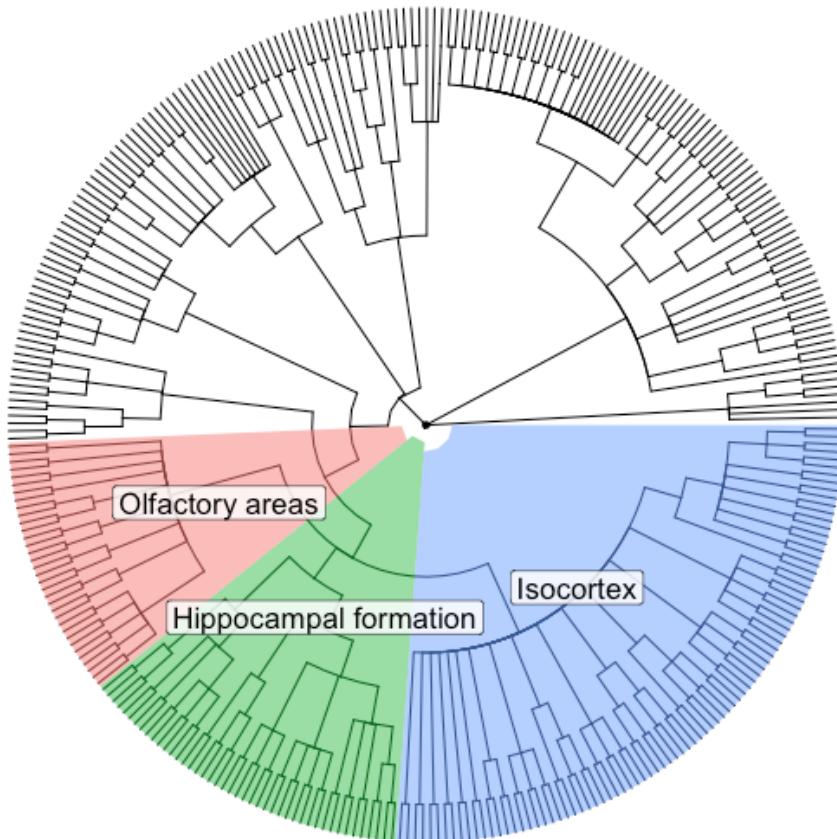
Subdividing the Grey Matter



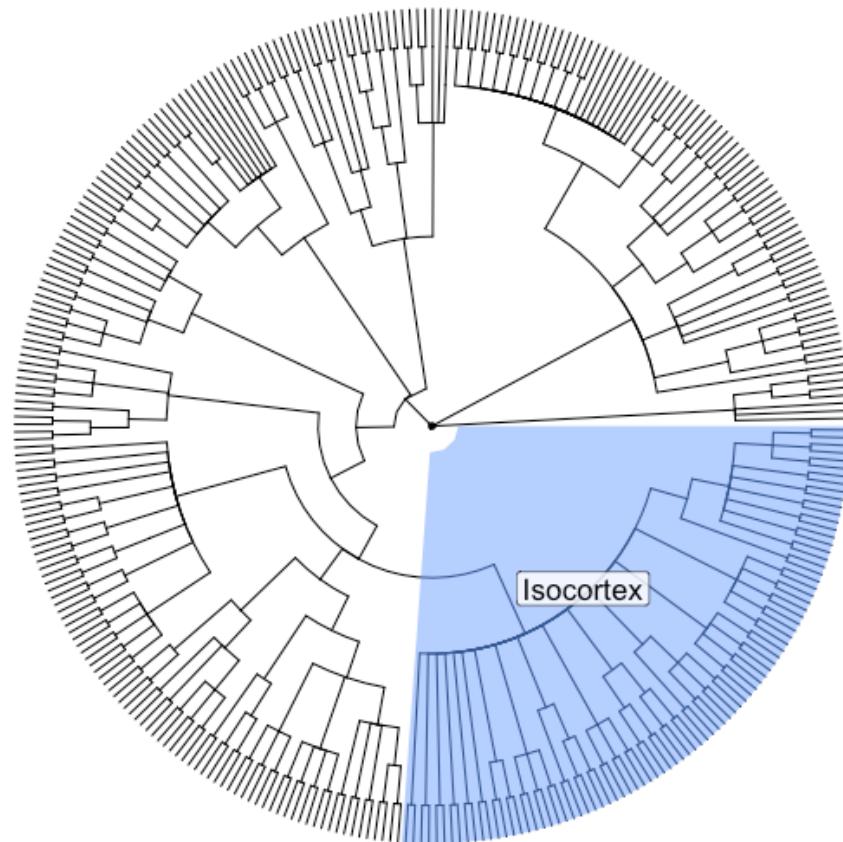
Subdividing the Grey Matter



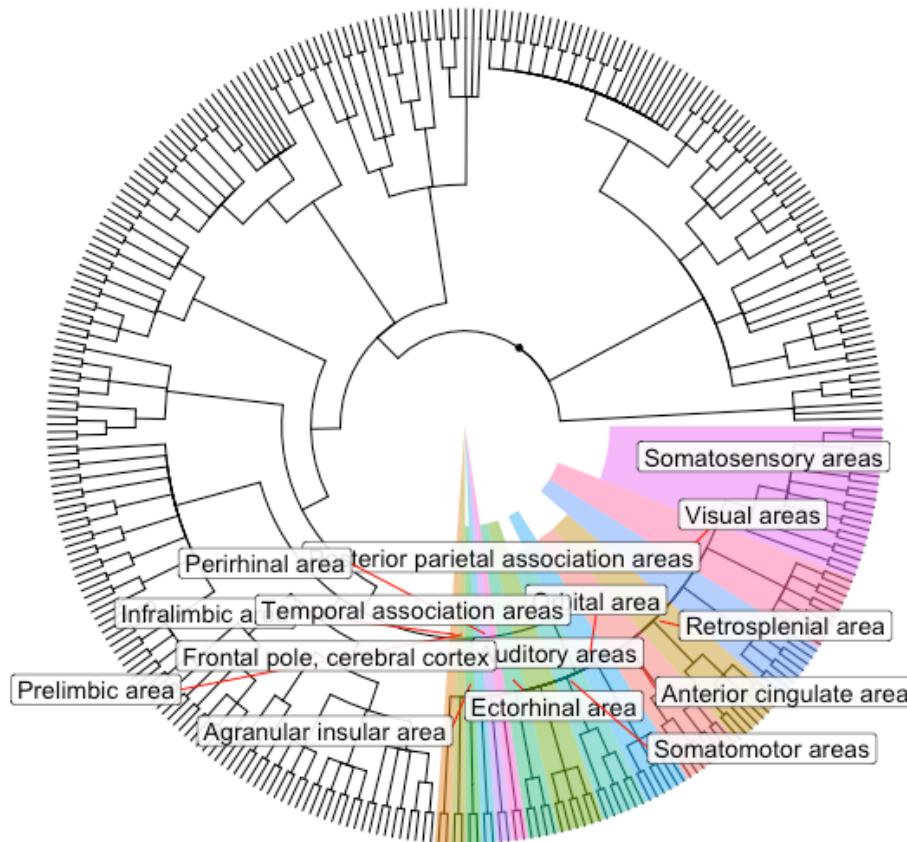
Subdividing the Cortex



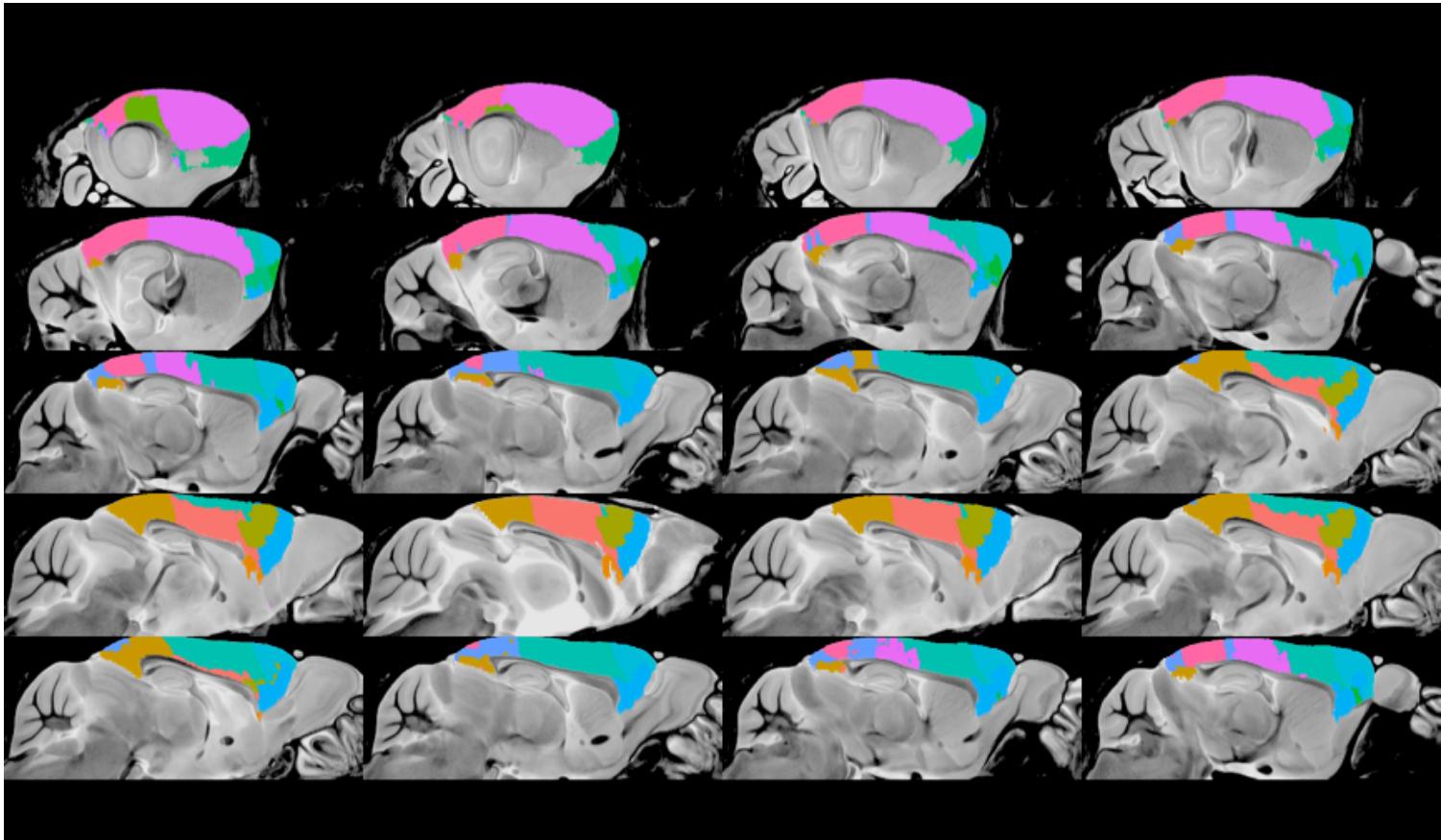
Subdividing the Cortex



Subdividing the Cortex



Subdividing the Cortex



Second Step: Pool by taxonomy

- Use the structure of the taxonomy to guide pooling
- Two main approaches:
 1. Pool across depths
 2. Pool toward immediate parent

Assess Five Models

- **No pooling:** chunk the data by structure, fit:

`y ~ eff with stan_lm then combine estimates`

Assess Five Models

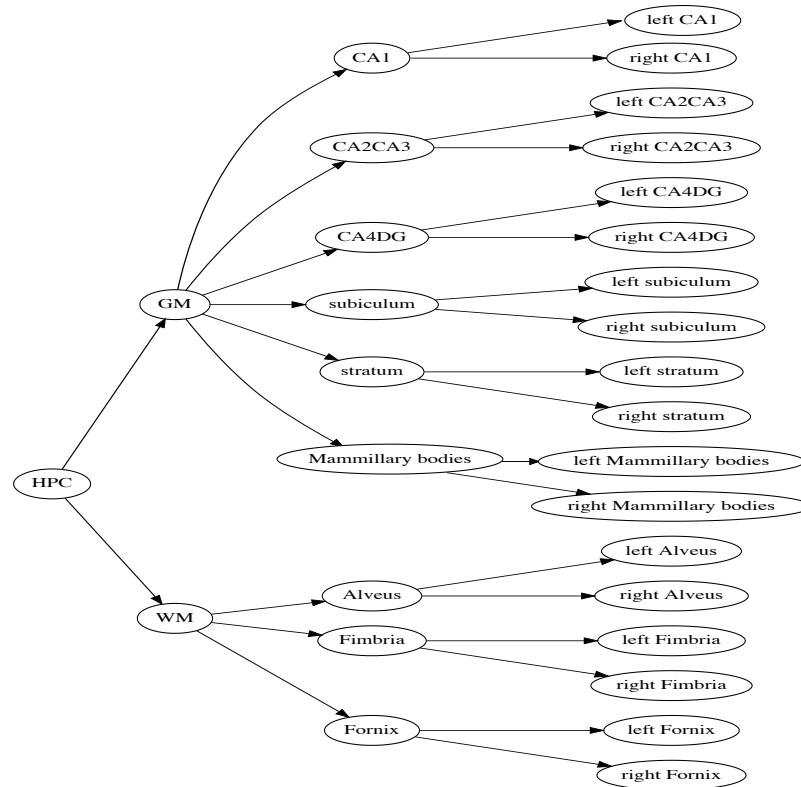
- **No pooling:** chunk the data by structure, fit:

$y \sim \text{eff}$ with `stan_lm` then combine estimates

- **Flat model:** pool across all structures, fit:

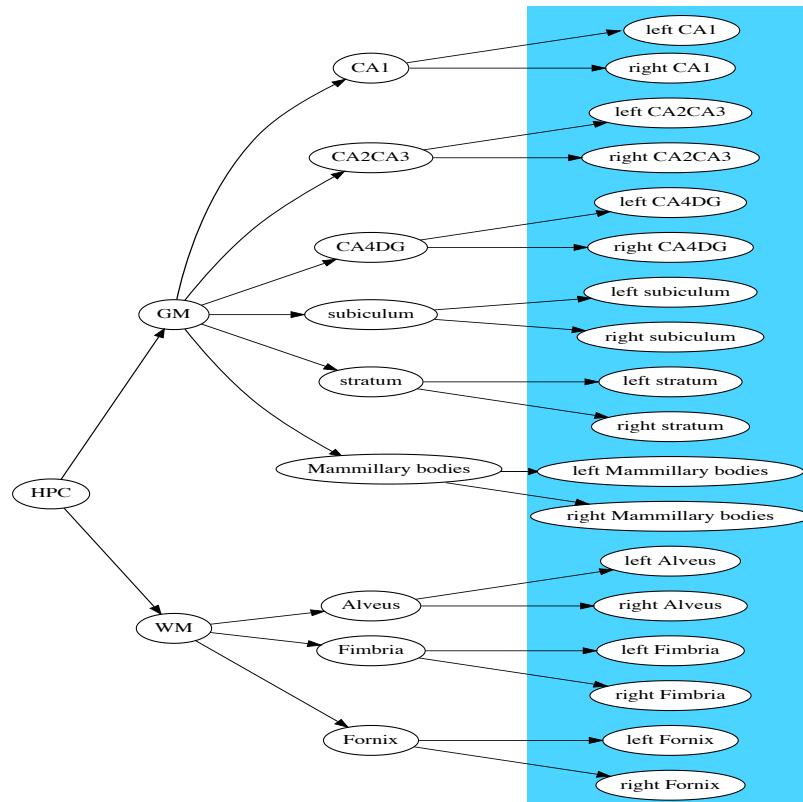
$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (1 \mid \text{ID})$ with `stan_lmer`

Flat Model



Flat Model

$$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (1 \mid \text{ID})$$



Assess Five Models

- **No pooling:** chunk the data by structure, fit:

$y \sim \text{eff}$ with `stan_lm` then combine estimates

- **Flat model:** pool across all structures, fit:

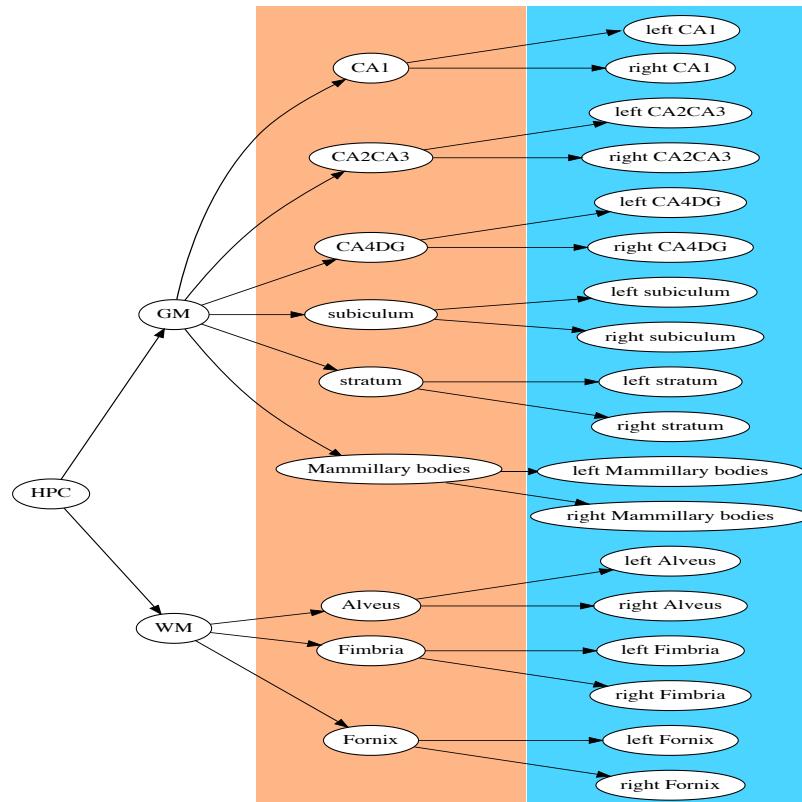
$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (1 \mid \text{ID})$ with `stan_lmer`

- **Parental model:** pool across all structures and add a pooled effect of parent, fit:

$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (\text{eff} \mid \text{parent}) + (1 \mid \text{ID})$

Parental Model

$$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (\text{eff} \mid \text{parent}) + (1 \mid \text{ID})$$



Assess Five Models

- **No pooling:** chunk the data by structure, fit:

$y \sim \text{eff}$ with `stan_lm` then combine estimates

- **Flat model:** pool across all structures, fit:

$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (1 \mid \text{ID})$ with `stan_lmer`

- **Parental model:** pool across all structures and add a pooled effect of parent, fit:

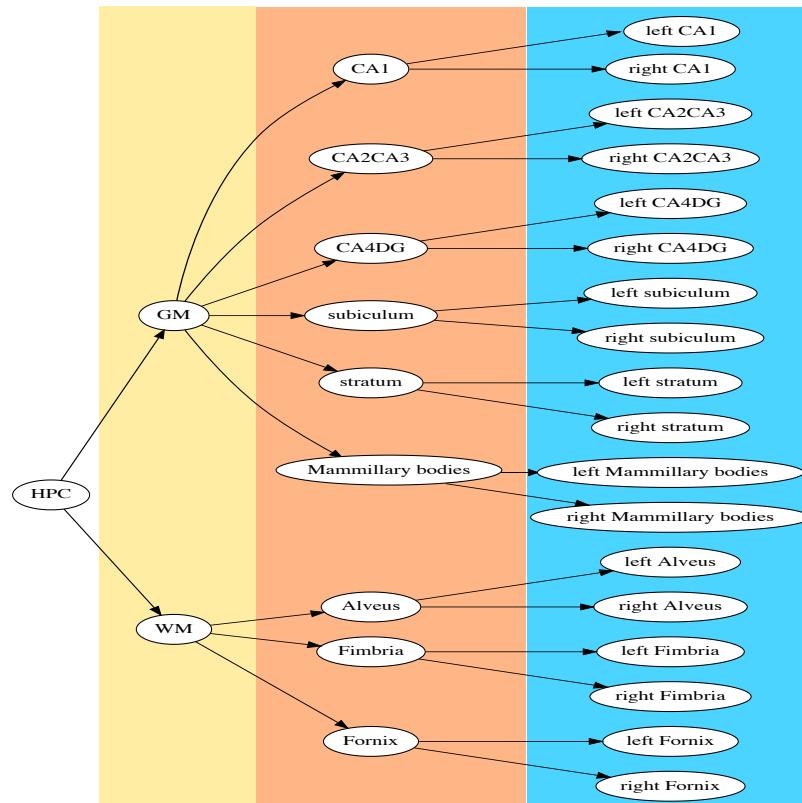
$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (\text{eff} \mid \text{parent}) + (1 \mid \text{ID})$

- **Grand-parental model:** add an effect for grand-parent, fit:

$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (\text{eff} \mid \text{parent}) + (\text{eff} \mid \text{gparent}) + (1 \mid \text{ID})$

Grand Parental Model

$$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (\text{eff} \mid \text{parent}) + (\text{eff} \mid \text{grandparent}) + (1 \mid \text{ID})$$



Assess Five Models

- **No pooling:** chunk the data by structure, fit:

$y \sim \text{eff}$ with `stan_lm` then combine estimates

- **Flat model:** pool across all structures, fit:

$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (1 \mid \text{ID})$ with `stan_lmer`

- **Parental model:** pool across all structures and add a pooled effect of parent, fit:

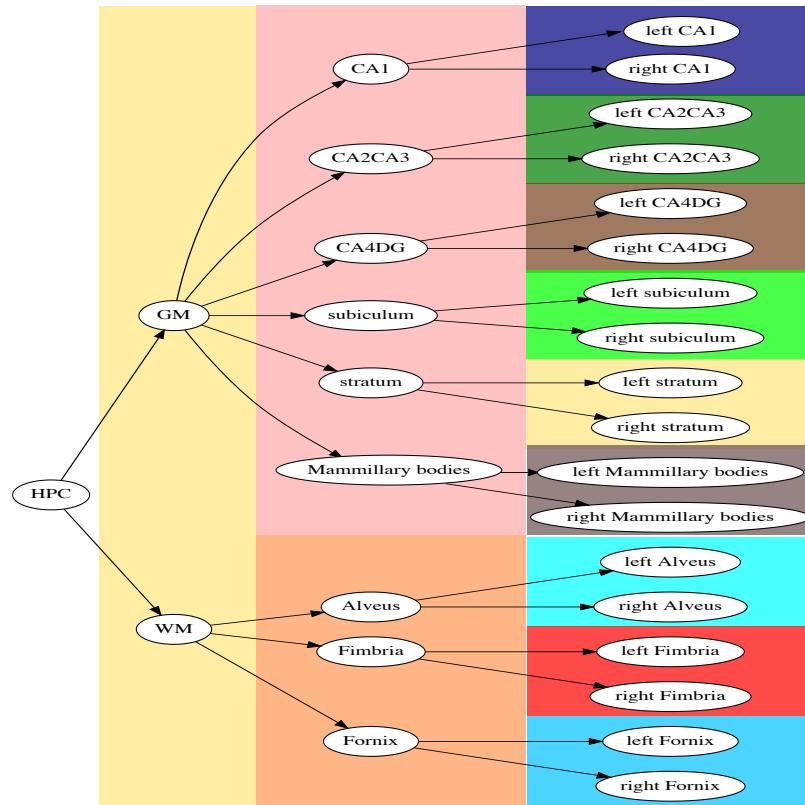
$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (\text{eff} \mid \text{parent}) + (1 \mid \text{ID})$

- **Grand-parental model:** add an effect for grand-parent, fit:

$y \sim \text{eff} + (\text{eff} \mid \text{structure}) + (\text{eff} \mid \text{parent}) + (\text{eff} \mid \text{gparent}) + (1 \mid \text{ID})$

- **Effect Diffusion Tree:** a pooling across branches.

Effect Diffusion Tree



Effect Diffusion Tree

Base Model

$$y_{is} = \beta \mathbf{x}_i^t + \beta_s \mathbf{x}_i^t + r_i + \epsilon_{is}$$

Effect Diffusion Tree

Base Model

$$y_{is} = \beta \mathbf{x}_i^t + \beta_s \mathbf{x}_i^t + r_i + \epsilon_{is}$$

Non-centered hierarchical effects

$$\beta_s = \Sigma^{1/2} \epsilon_s$$

Effect Diffusion Tree

Base Model

$$y_{is} = \beta \mathbf{x}_i^t + \beta_s \mathbf{x}_i^t + r_i + \epsilon_{is}$$

Non-centered hierarchical effects

$$\beta_s = \Sigma^{1/2} \epsilon_s$$

Effect diffusion model

$$\beta_s = \beta_{p_s} + \Sigma^{1/2} \epsilon_s$$

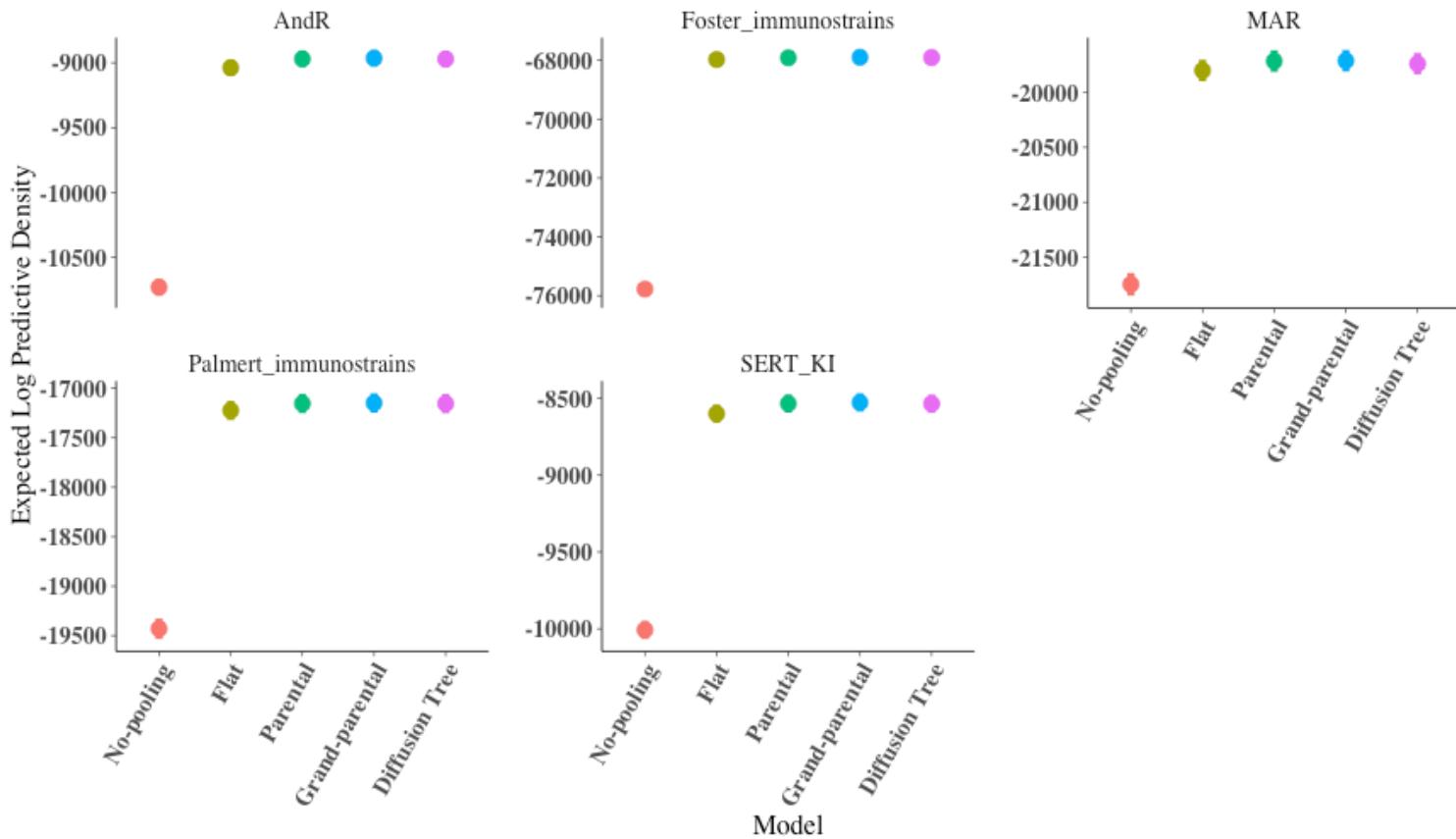
Simulation Results

- Simulated from two data generating processes
- When simulating from effect diffusion prior, the effect diffusion model performs better
- When simulating from a simpler DGP, all hierarchical models perform similarly

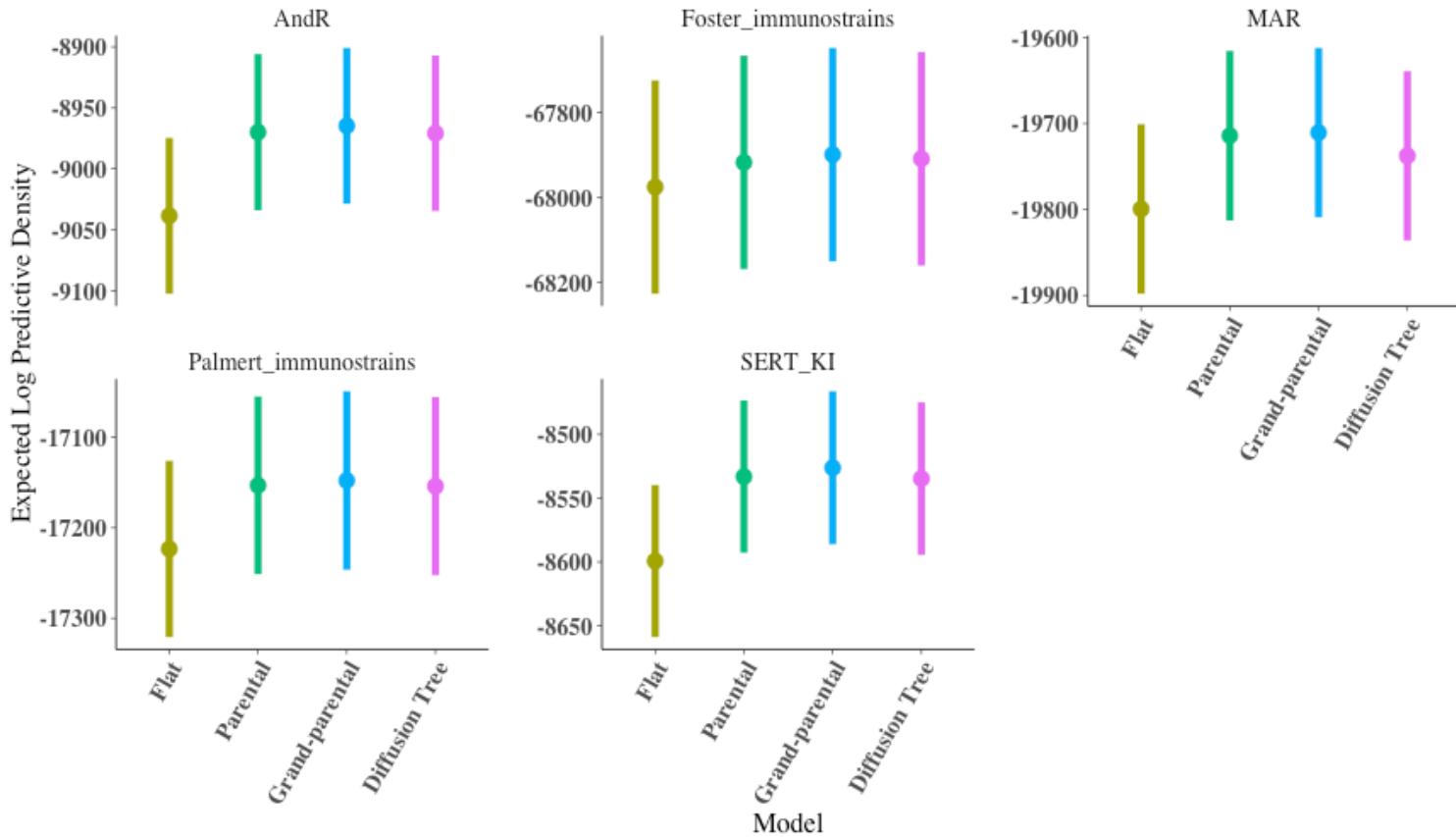
Real Data Results

- Each study collects controls, so we have many replicates of control mice.
- Can examine each set of controls for sex differences
- Examined five studies
 1. AndR - 20 mice
 2. Foster - 158 mice
 3. MAR - 45 mice
 4. Palmert - 40 mice
 5. SERT_KI - 20 mice
- Estimates from each study were compared against the average of the other four studies.
- Assess predictive performance
- Assess type S error
- Assess effect consistency across replicates.

Compare Loo



Compare Loo



Claims with confidence

No-pooling	Flat	Parental	Grand-parental	Diffusion Tree
126	47.8	122	18.8	68.8

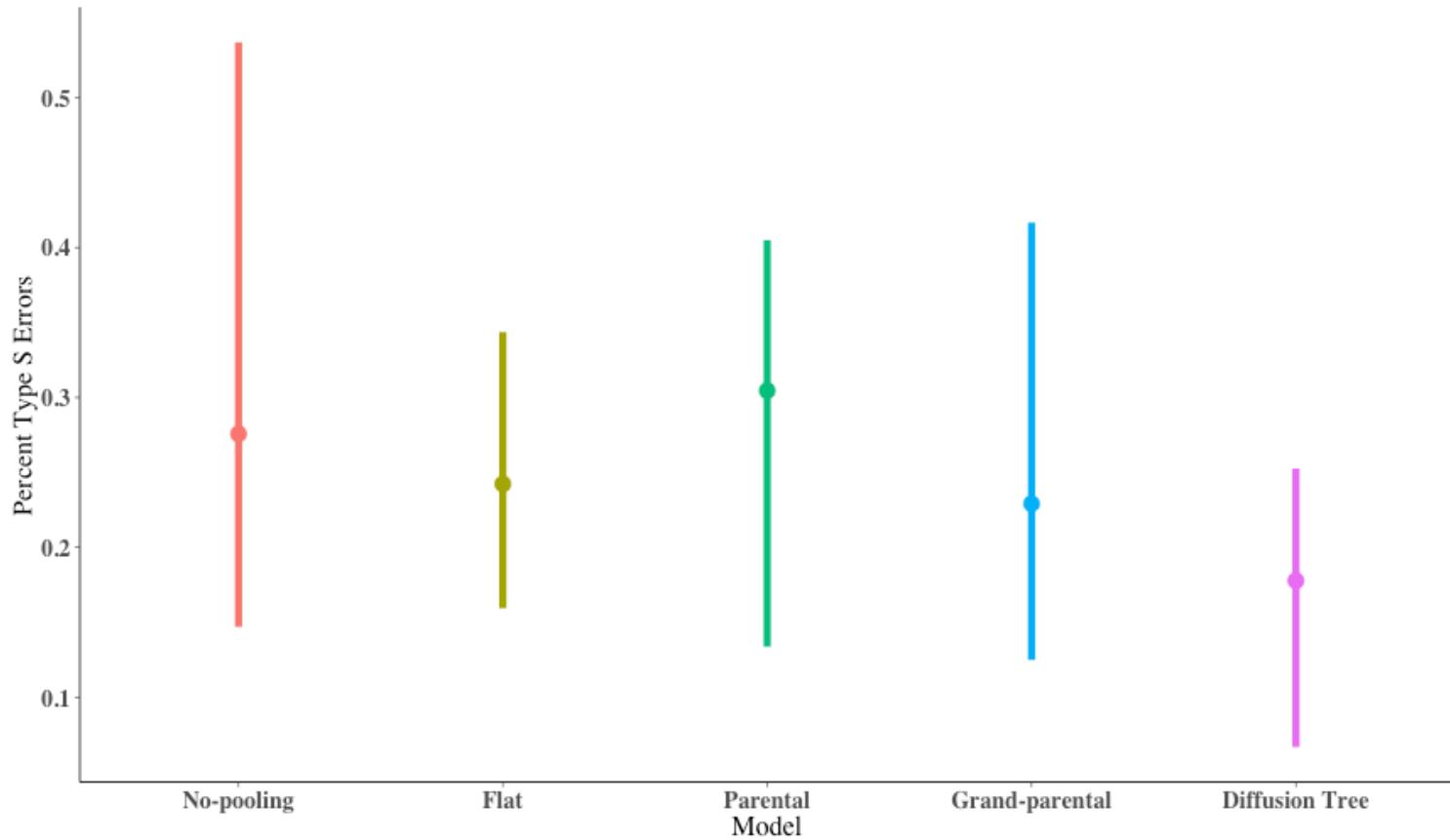
- Claims with confidence where 90% credible interval doesn't bound zero
- No-pooling and parental models make the most claims with confidence
- Grand-parental model makes very few

Set similarity of claims with confidence

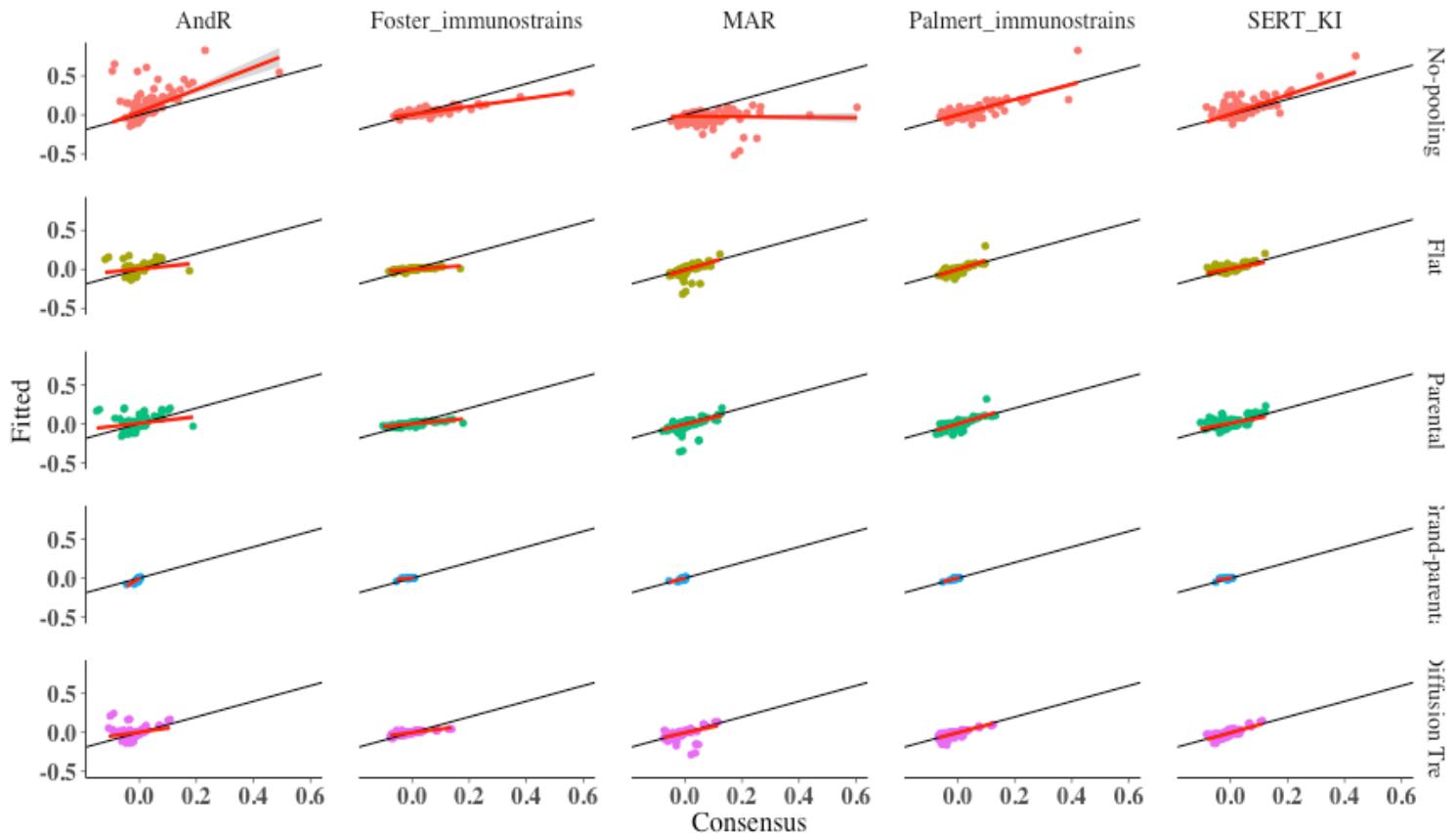
No-pooling	Flat	Parental	Grand-parental	Diffusion Tree
0.341	0.118	0.283	0.524	0.182

- Mean pairwise Jaccard similarity of recovered structures
- The grand-parental model has the highest mean similarity
- The no-pooling model has high similarity
- Flat and effect diffusion have the lowest set similarities

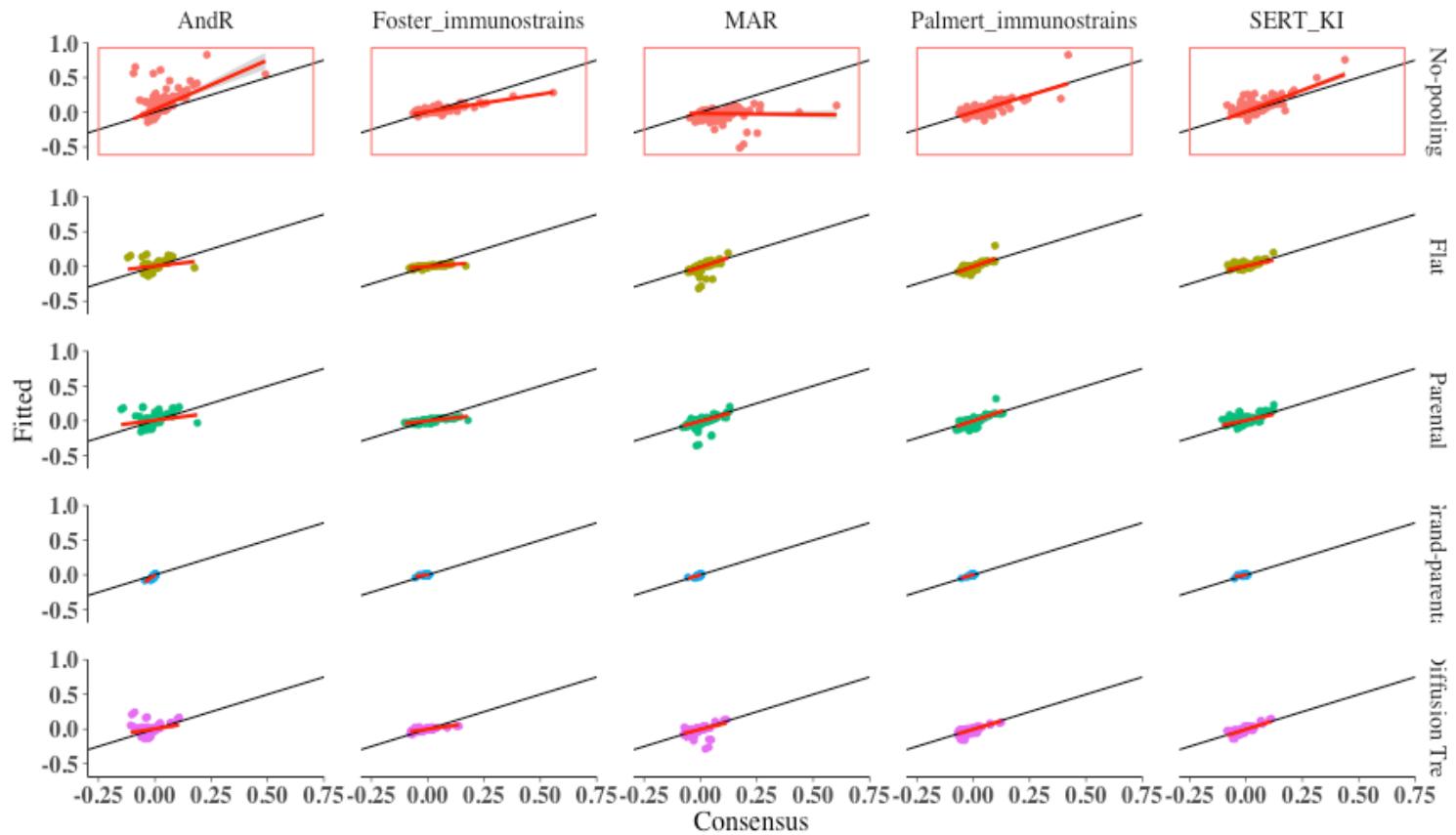
Type S errors



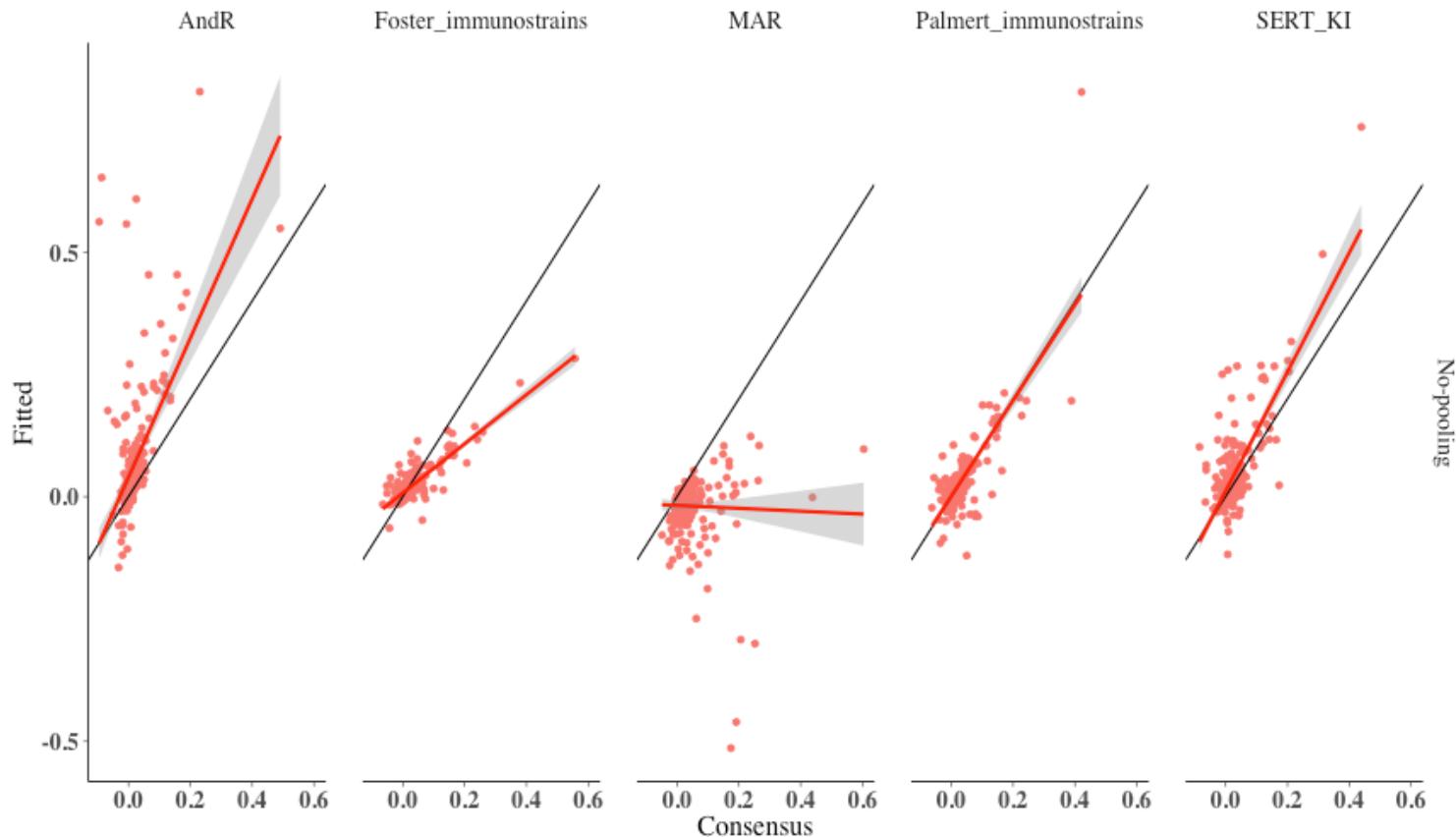
Effect Correlation



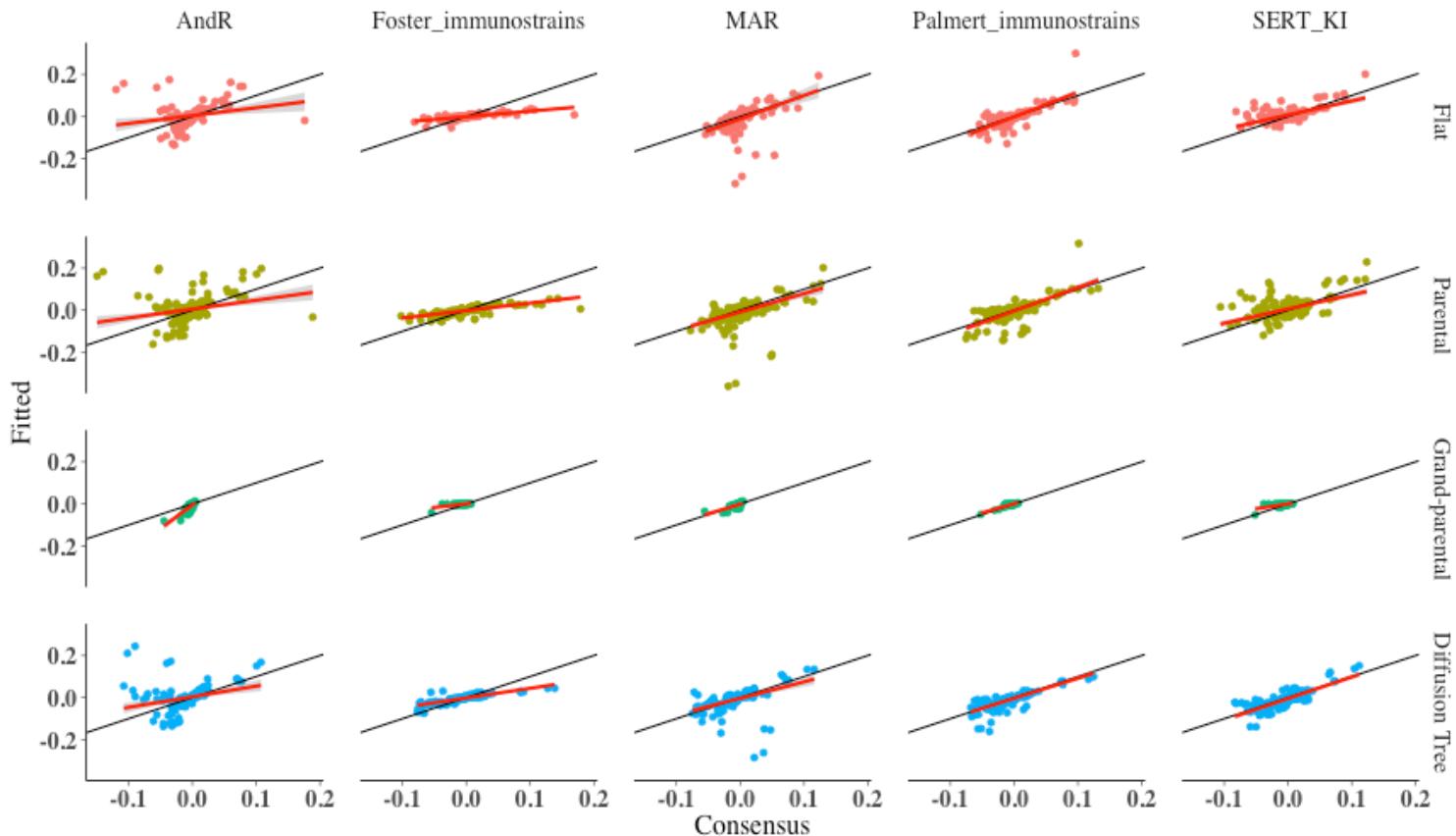
Effect Correlation



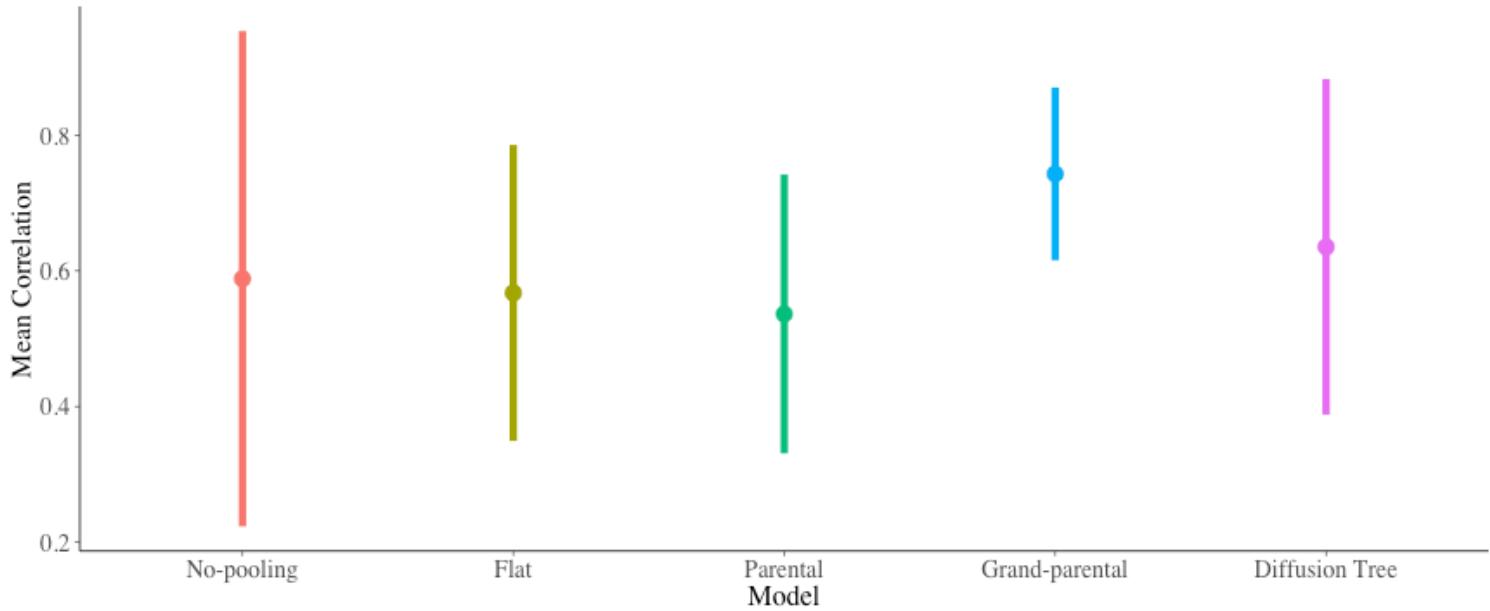
Effect Correlation



Effect Correlation



Effect Correlation



- The grand-parental model had the best agreement between individual studies and the average of the others. (I'm suspicious)
- No-pooling had the most variance
- The diffusion tree outperformed no-pooling, flat, and parental models.

Next Steps

- Identify the circumstances under which each model is most useful
- Explore other notions of distance, perhaps using gaussian processes
- Scale up - move from 10^2 structures to 10^7 voxels.
- Regularize
- Aggregate

Take Aways

- Region based neuroscience can benefit from hierarchical modelling.
- All hierarchical models outperform no-pooling
- We can slightly improve performance when respecting the brains taxonomic structure
- It is unclear how exactly to model the taxonomy
- The effect diffusion performs as well as simpler methods, but can model more complex trees
- Lots to be done.

Take Aways

- Region based neuroscience can benefit from hierarchical modelling
- All hierarchical models outperform no-pooling
- We can slightly improve performance when respecting the brains taxonomic structure
- It is unclear how exactly to model the taxonomy
- The effect diffusion performs as well as simpler methods, but can model more complex trees
- Lots to be done.

Contact me

- Chris Hammill
- twitter: @cfhammill
- github: @cfhammill
- website: cfhammill.github.io