Examining the Modulating Effect(?) of Sex in ASD Neuroanatomy

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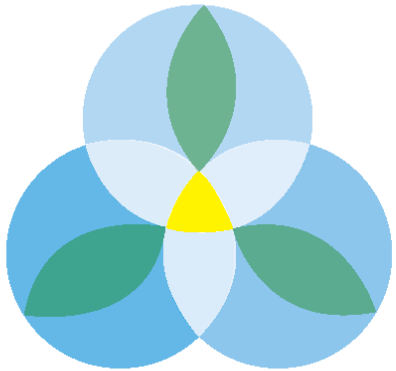
Caveat Auditor!

This presentation is about methods, all results should be treated as placeholders!

POND



POND NETWORK

Province of Ontario Neurodevelopmental Disorders

- The Province of Ontario Neurodevelopmental Disorders Network
- Cross disorder initiative to study ASD, attention deficit/hyperactivity disorder, obsessive compulsive disorder, and intellectual disability
- Sites in Toronto, Hamilton, London, and Kingston
- Battery of phenotyping with behaviour, genetics, and brain imaging

Intro

- Autism Spectrum Disorder (ASD) is characterized by difficulties in social communication presenting at an early age
- **ASD effects 2-5 times as many males as females**
- Studies examining the differential effect of ASD on neuroanatomy in males and females are typically underpowered.
- We are presently examining the differential effect of ASD in both sexes with a large (the largest?) cohort of ASD females acquired at a single site.

So why is ASD so much less common in females?

Why the diagnosis differences?

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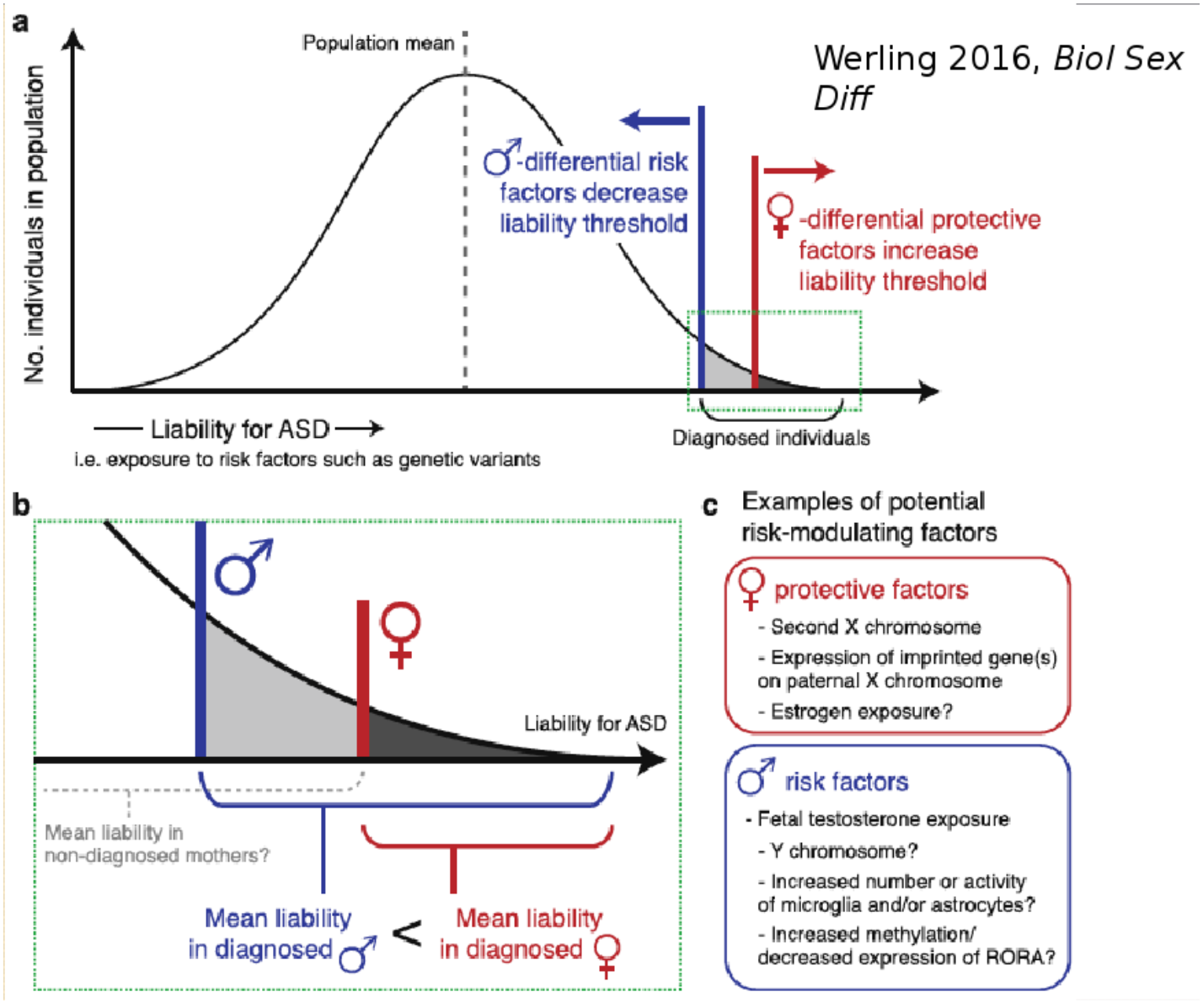
Why the diagnosis differences?

- Differences in number of risk factors?
- Some evidence of increased copy number variant load in females with ASD relative to males
- Differences in neurobiological etiology?
- Broad range of experiments showing qualitative differences between males and females with ASD

Hypothesis 1: Difference in Number of Risk Factors



Hypothesis 2: Sex Dependent Risk Factors

- Maybe the risk factors for ASD are just different for females

Two Models

- Differences could be quantitative: females with ASD have larger cortical differences

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- Differences could be qualitative: females with ASD have a different pattern of cortical differences

Pointed hypotheses

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- alternatively, if the null holds you'll get as many or more spatial locations where the male effect is larger
- If the qualitative model is true then the spatial distribution of female conditional effects will be less correlated with the male effects than you'd expect by chance.
- alternatively, if the signals are more correlated than you expect there's no evidence that the whole brain spatial distribution is different.

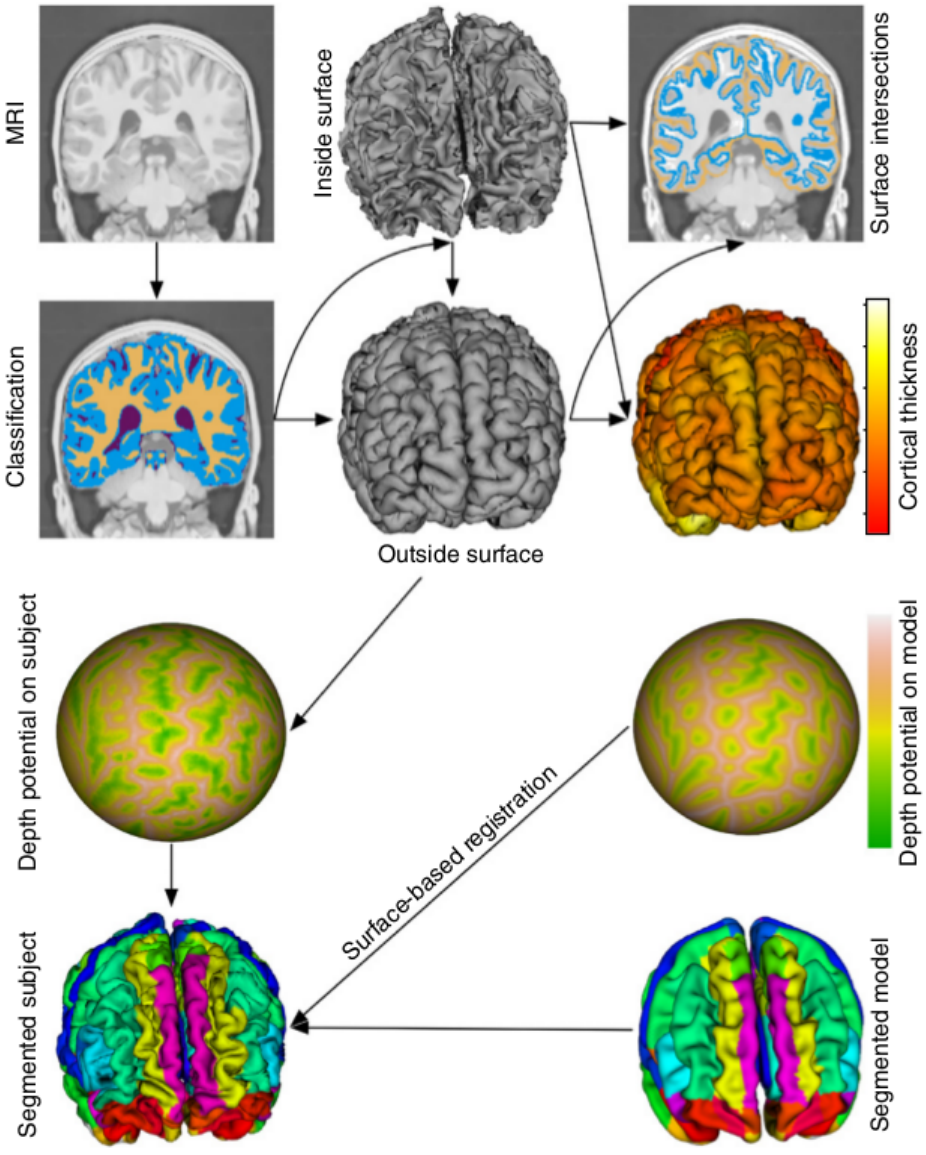
Spatial Patterns of What?

A brief digression into CIVET

CIVET

- Pipeline for measuring anything cortical in humans
- Starts with some preprocessing
- Subjects are registered to ICBM
- Tissue classification into grey matter, white matter, and CSF
- A surface is fit to the grey-white interface
- The surface is expanded to the grey-CSF interface
- Cortical thickness, area, volume, and curvature can be computed from the two surfaces.

CIVET


MRI
Inside surface
Surface intersections
Classification
Cortical thickness
Outside surface
Depth potential on subject
Depth potential on model
Surface-based registration
Segmented subject
Segmented model

The Data

- Assembled from POND data and Margot Taylor's subjects
- Grand total of 1356 T1 scans (many longitudinal)
- After CIVET QC and de-longitudinalization 680 scans remain

- **226** ASD males
- **193** control males
- **59** ASD females
- **202** control females

I have my measures of interest, what now?

Dealing with non-experimental data

- Humans are highly variable
- ASD status is not randomly assigned

- Need to fend off omitted variable bias
- Need to deal with missing data
- Need to account for covariate heterogeneity
- Need to choose the best model

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Omitted variable bias

- The bias in parameter estimates introduced when important information is left out of the model.
- Key covariates:
  1. Subject age
  2. IQ
  3. Whole brain volume

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Missing Data

- Many subjects are missing IQ ($\sim$ 13%)
- Most principled solution is Multiple Imputation

Multiple Imputation in Brief

- A distribution of IQ given the other covariates is generated for the data.
- Draws from this distribution are used to complete the data set
- Do this multiple (e.g. 5) times
- Run your analysis on each imputed set
- Pool results across sets

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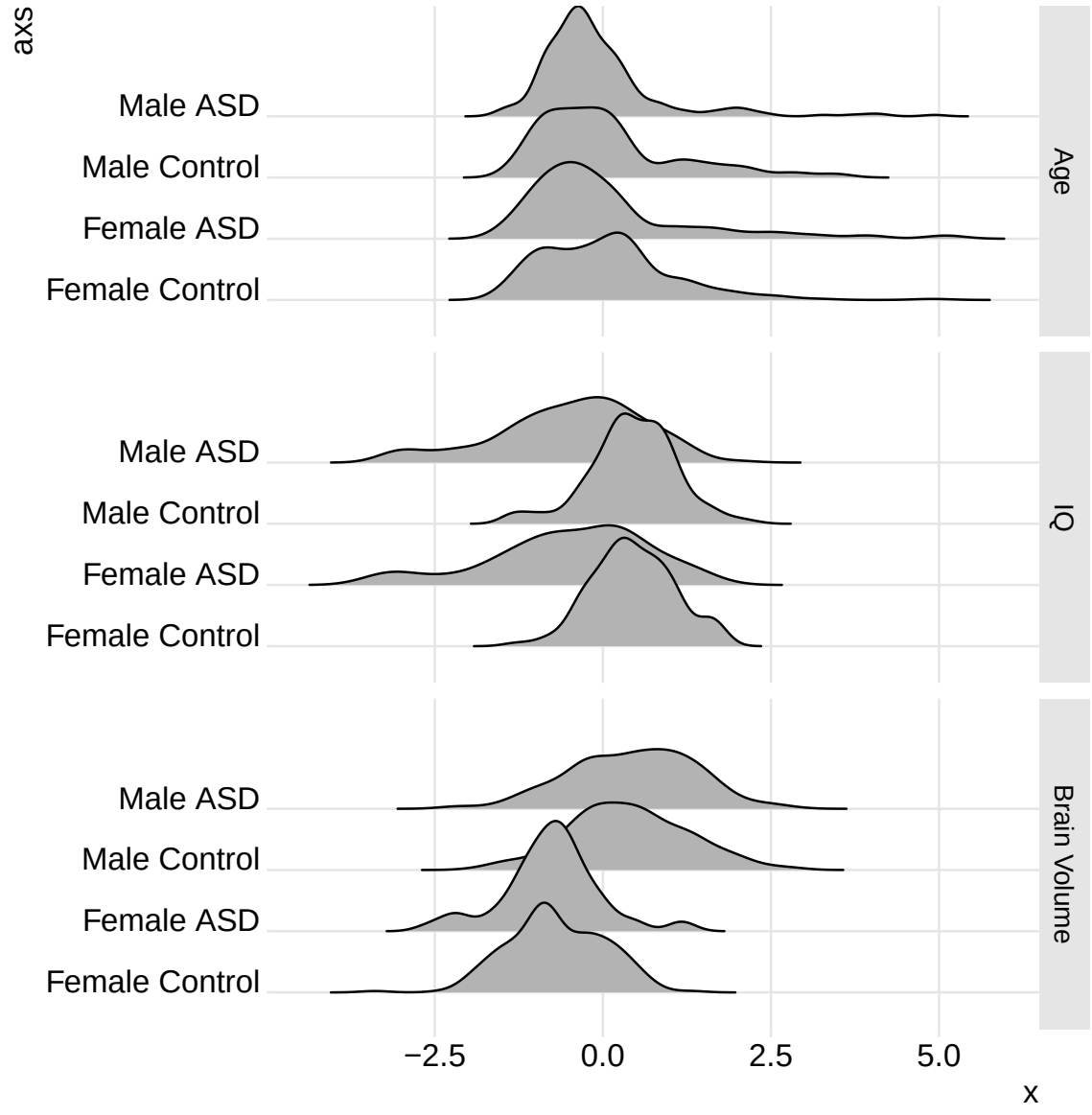
Accounting for Covariate Heterogeneity

- Mis-matches in covariate distributions biases analysis
- One potential solution is matching preprocessing
- In ideal cases reduces bias and the degree to which the choice of model impacts parameter estimates
- Many approaches, nearest neighbour matching, inverse probability weighting, coarsened exact matching, and full matching to name a few
- I used full matching

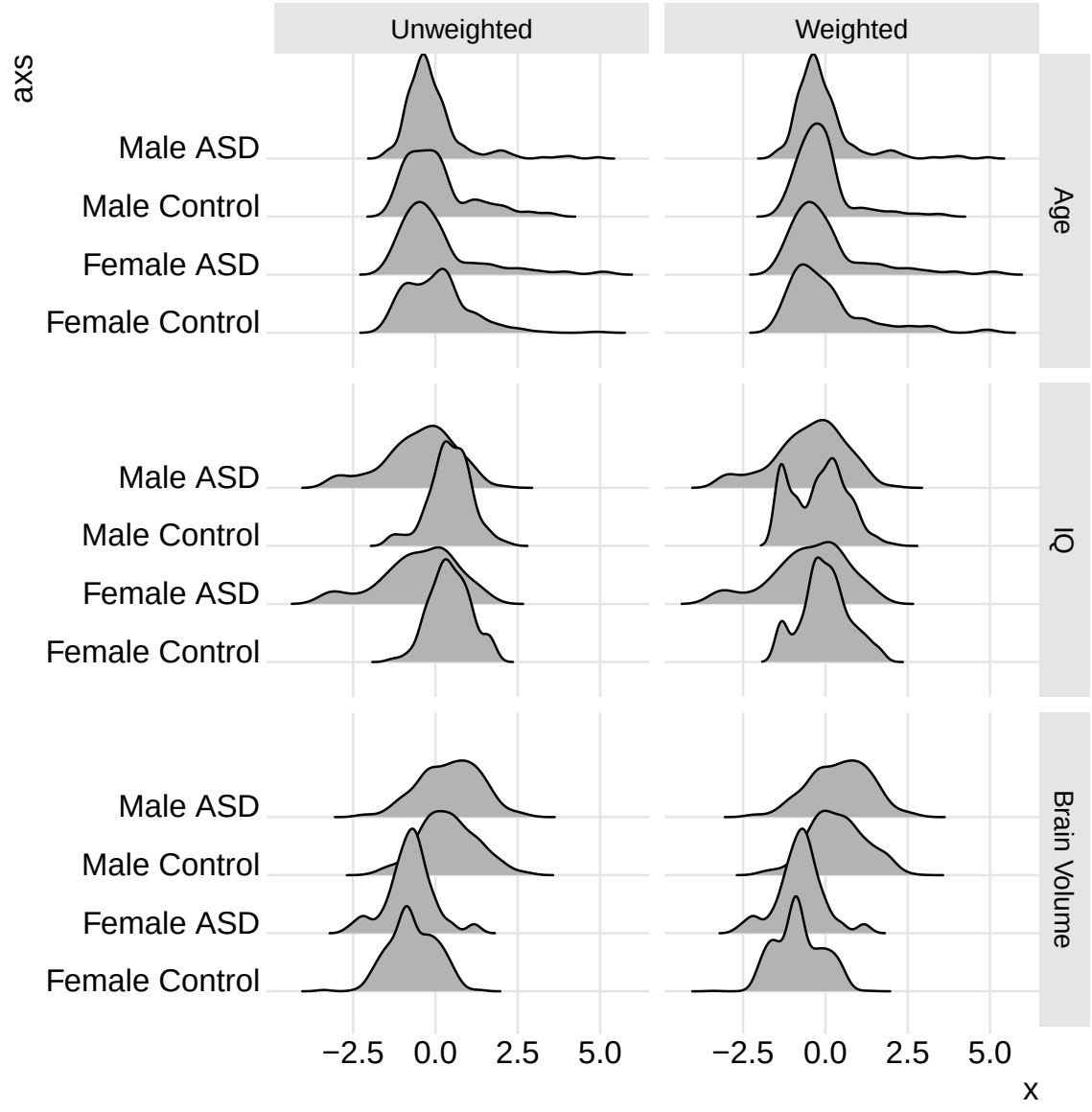
Full matching

- Choose a distance measure, most common are propensity score and mahalanobis distances.
- I chose weighted euclidean matching to impose structure on the matches
- I wanted age matched really well, IQ matched to a lesser degree and brain volume matched the least well
- Full matching matches each ASD to some number of controls
- Controls are re-weighted by their number of matches

Before Matching



After Matching



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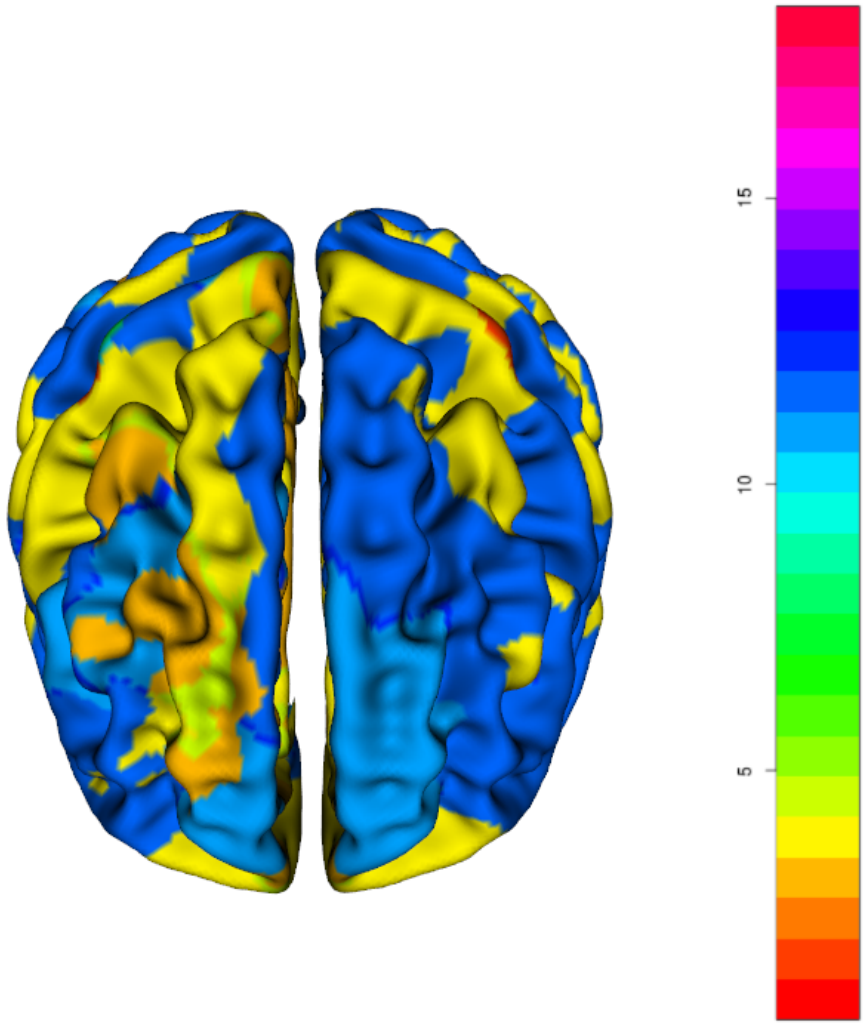
Choosing the best model

- Need to choose the best parametric form for the model
- Should age be linear or polynomial?
- Should brain volume or an exponentiated version be used?
- Should interactions between sex and the other covariates be included?
- Total of 18 models to test at each measure

Choosing the best model

- Fit each competing model to the cortical measures
- Compute the vertex-wise AIC
- Compute the evidence ratio at each vertex
- Choose the model with the lowest median evidence ratio

Model Selection



Top Models

- Common to all models
  $sex + dx + sex * dx + scanner + iq + age$

- Thickness: $\sim age^2 + bv^{1/3}$ Median Evidence Ratio (1.2)
- Area: $\sim bv^{2/3}$ Median Evidence Ratio (18.9)
- Volume: $\sim bv^{1/3}$ Median Evidence Ratio (3.5)
- Curvature: $\sim bv$ Median Evidence Ratio (9.8)

Computing Conditional Effects

With the fitted model how do we get the conditional effects?

- $\left.\frac{\partial Y}{\partial dx}\right|_{sex=M} = \beta_{dx}$
- $\left.\frac{\partial Y}{\partial dx}\right|_{sex=F} = \beta_{dx} + \beta_{sex*dx}$

Inference

- The statistic of interest was computed with the original data and averaged across imputed sets
- Randomization distributions were generated by permuting the sex label of each subject
- 1000 permutations were generated
- *Imputation and matching were performed before permutation (debatable)*
- Analysis was performed with each of five imputed data sets against the *same* permutation.
- The mean statistic of interest was averaged for each permutation across the imputed data sets.

Evaluating the Quantitative Model

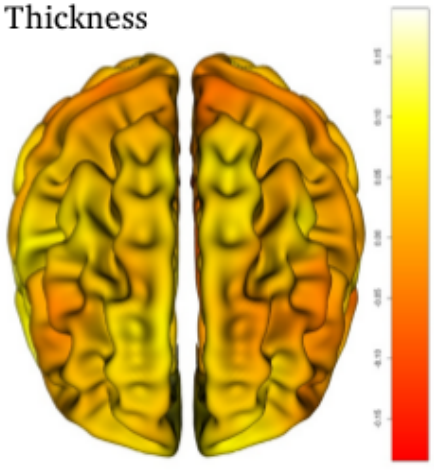
- At each vertex compute if β_{dx} and β_{sex*dx} have the same sign (sign condordance)
- If they do, the conditional effect in females has a greater magnitude and the same sign as the male effect.
- Sum the number of vertices where this is true
- Test against a randomization distribution of proportion of concordant vertices

Multiple Thresholds

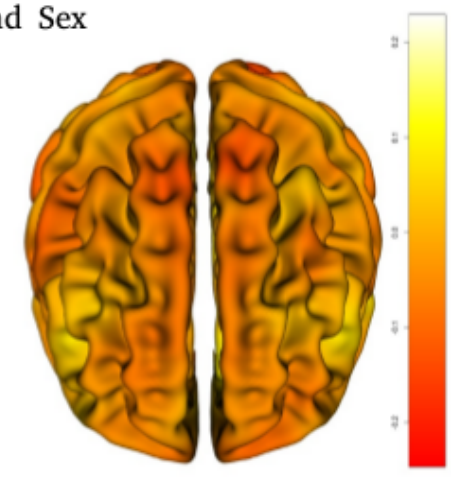
- Maybe the quantitative effect only exists at stronger effect sizes
- Apply thresholds from weak to strong, evaluating the proportion of concordant vertices at each threshold

Concordances

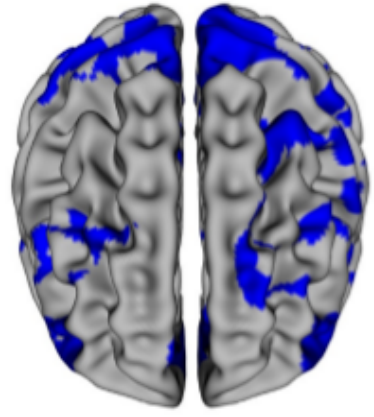
Male Effect of ASD on Thickness



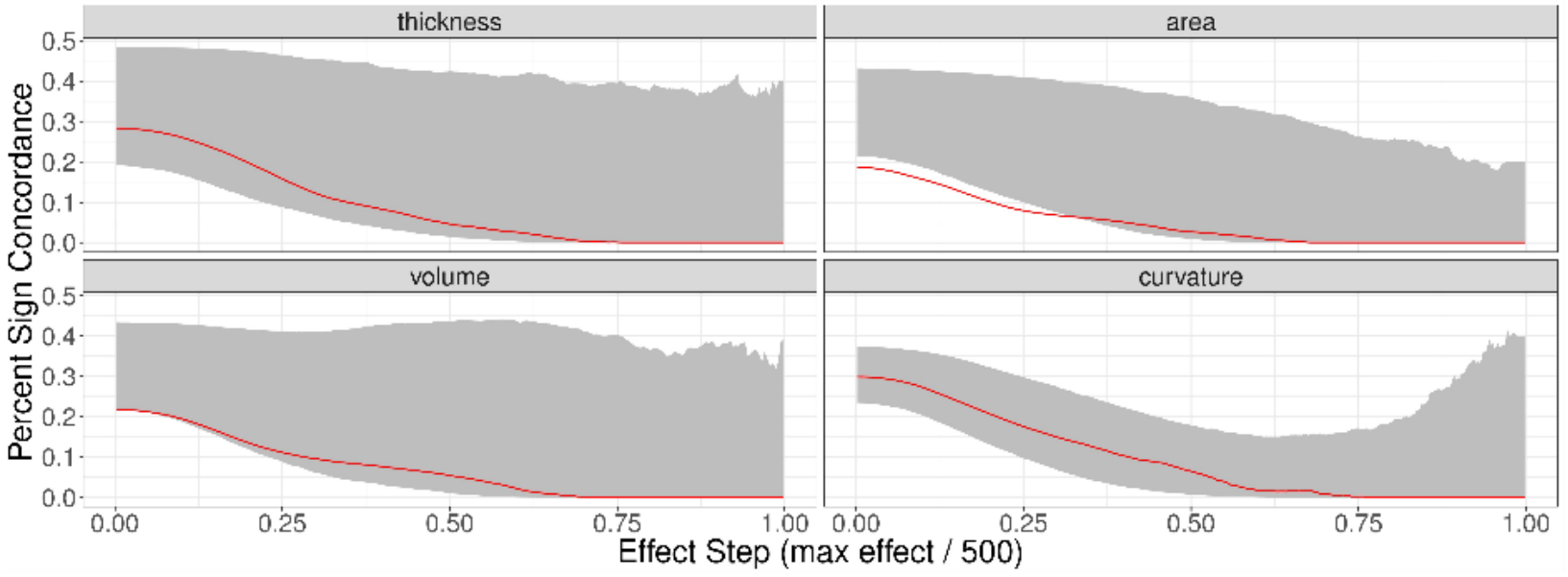
Interaction of ASD and Sex



Vertices with Concordant Signs



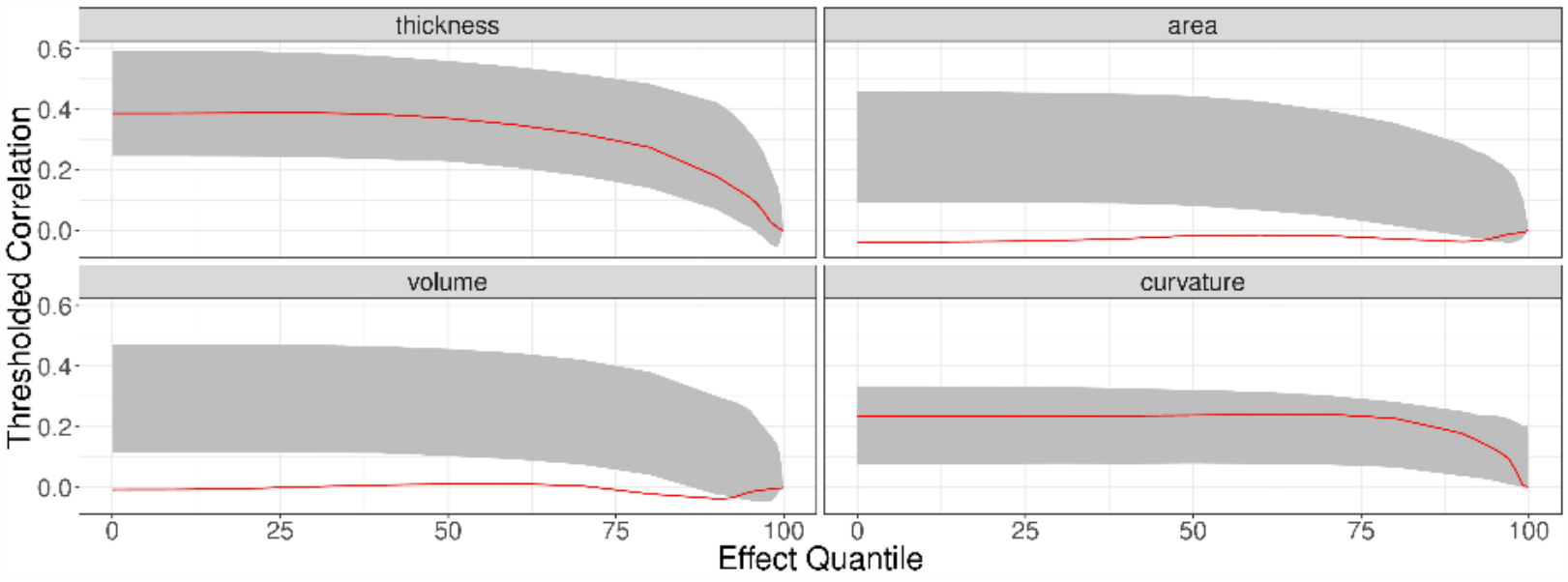
Randomization distributions



Evaluation the Qualitative Model

- Examine the correlation of measures across the cortex
- Do it at matched quantiles of conditional male and female effects
- Evaluate against a randomization distribution

Randomization distributions



Looming Questions

- What is the right way to approach matching, which distance measure, which technique, should I trim covariate distributions
- What about IQ, they're acquired with different instruments, should this be accounted for?
- When should I match, before or after randomization
- When should I impute, before or after randomization
- At what spatial scale should I do model selection? Vertex, region, hemisphere, whole brain?
- Is it worth using longitudinal data with a random effect model?

Thanks To

- Meng-Chuan Lai
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Thoughts?