Heritability of subcortical volumes in the adolescent brain

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Subcortical heritability through lifetime

# Subcortical volumes associated with psychological disorders

- Major depressive disorder - hippocampus, putamen, caudate nucleus[1]
- Schizophrenia - anterior cingulate, hippocampus/amygdala, thalamus, insula[2]
- Anxiety - amygdala, insula, anterior cingulate cortex[3]

Figure 1: Subcortical regions highlighted in red

Subcortical volumes are heritable

- In young adults and adults[4]
- Heritability of head size changes through lifespan[5]

Figure 2: Heritability across brain volumes, Red means highly heritable

Extending the trajectory

▶ Regional heritability varies through lifetime in adults[4]

▶ Want to extend their scale to younger years

▶ **Q: Are regional volumes heritabile in adolescents (9-10 years old)?**

Figure 3: Heritability of brain regions for different
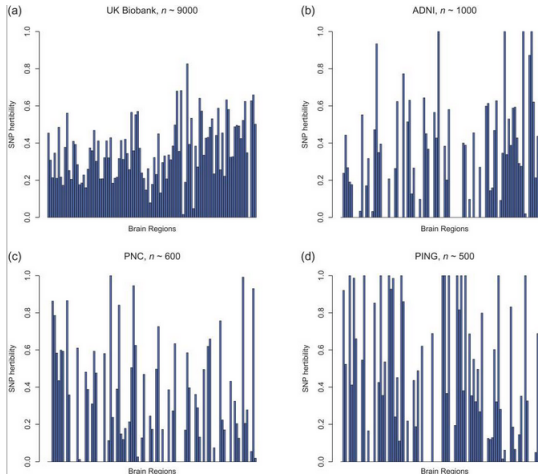
Difficulties in extending timeline

Difficult to estimate since the largest dataset is multiple sites

- ▶ Adolescent Brain Cognitive Development study (ABCD)
- ▶ Taken over 22 sites
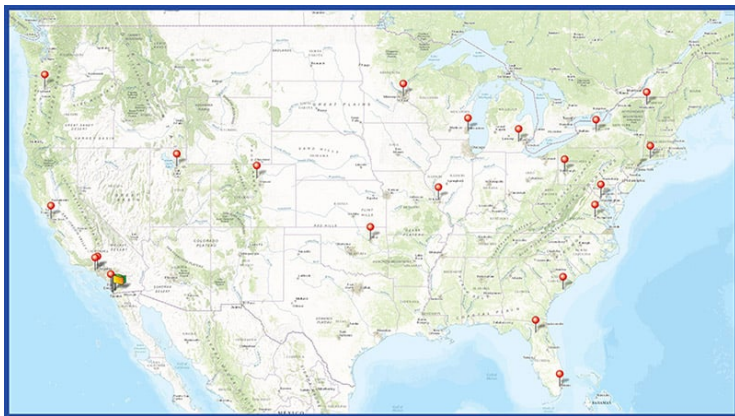- ▶ Confounding with scanner and site effects

Figure 4: Map of ABCD sites

Variance component models to estimate heritability

Linear model explaining genetic influence

$$Y = X_g \beta_g + X_d \beta_d + \epsilon$$

▶ X_d is demographics (i.e. age, sex, etc.)
▶ X_g is ($\#subjects \times \#SNPs$) genetic data
($\#SNPs >> \#subjects$)

Variance component models for heritability

▶ Assume SNPs $\beta_g \sim N(0, \sigma_g^2(2f(1-f))^{-1}/m)$
▶ Genetic relatedness matrix (GRM) is genetic correlation between individuals ($GRM = X_g^{stand} X_g^{stand,T}/\#SNPs$)
▶ PC_j is the jth pc of the GRM
▶ Then the model reduces to

$$Y = X_d \beta_d + \sum_{i=1}^{k} \lambda_i PC_i + \epsilon$$

$$Var(\epsilon) \sim \sigma_g^2 GRM + \sigma_e^2 I + \sum_{i=1}^{k} \delta_i PC_i PC_i'$$

▶ Interested in heritability $:= \frac{\sigma_g^2}{\sigma_g^2 + \sigma_e^2}$

AdjHE extension accounts for site effects in second moment

▶ Estimate σ_g^2, σ_e^2 via Restricted Maximum Likielihood (REML) or method of moments (MOM)

▶ Previously, created closed form solution to MOM (AdjHE)

▶ Next, control for site effects into MOM

▶ Phenotypes measured over multiple sites/scanners but same protocol assume only mean affected

▶ X_s site mebership matrix

$$EY = X_d\beta_d + X_S\beta_S + \sum \lambda_i PC_i$$
$$Var(Y) = \sigma_g^2 GRM + \sum \delta_i PC_i PC_i' + \sigma_e^2 I$$

AdjHE extension accounts for site effects in second moment

▶ Many sites leads to estimation of high dim β_S
▶ First k PCs of GRM correlate to site membership
▶ Additionally assume site effect iid with variance σ_S^2

$$EY = X_d \beta_d + \sum \lambda_i PC_i$$

$$Var(Y) = \sigma_g^2 GRM + \sigma_S^2 S + \sum \delta_i PC_i PC_i' + \sigma_e^2 I$$

▶ Heritability: genetic influence (σ_g^2) vs environment (σ_e^2)
▶ Closed form OLS solution on 2nd moment

Outperforms existing methods adjusting for site effects

- ▶ Other estimators necessitate site indep of genetics
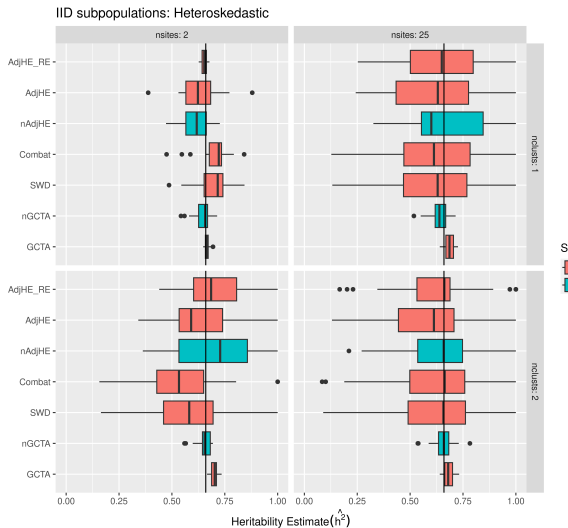- ▶ up to 4x faster computation (with minimal optimization)

Figure 5: Simulated comparisons

Multiple subcortical volumes highly heritable in adolescence

Multiple subcortical volumes highly heritable in adolescence

▶ Lowest heritability in oldest part of brain: brain stem
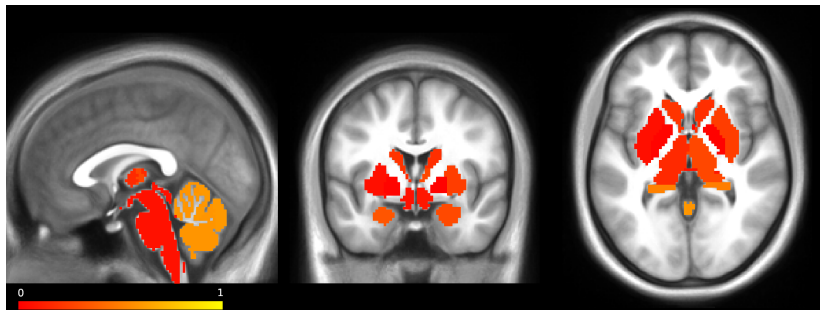▶ Higher heritability in outer regions: hippocampus, cerrebellum

Figure 6: Heritability estimates visualized on the brain

Future extensions and applications

▶ Estimate heritability of functional networks (and their topographies)
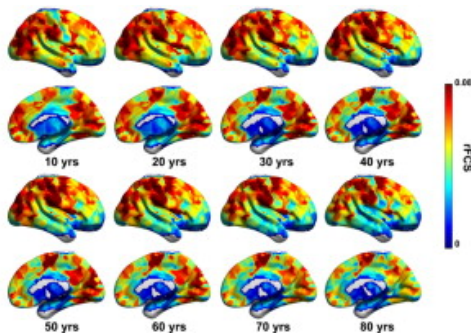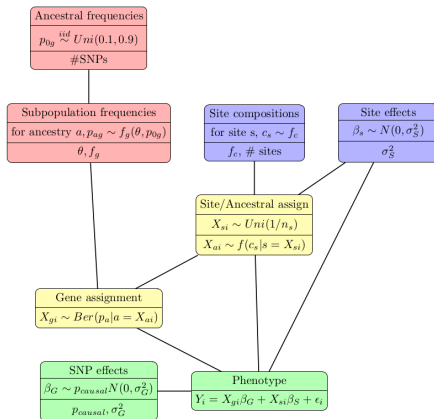▶ Extend estimation to multivariate traits

Figure 7: Functional topologies as a function of age

Image credit Cao et al. 2014

Toolbox

Simulation features


Figure 8: Simulation diagram

- ▶ Simulates phenotypes from existing or simulated GWAS data
- ▶ Control heritability across distinct genetic clusters
- ▶ Control shared vs nonshared SNP effects across genetic clusters

Estimation features

- GREML (via GCTA wrapper)
- Method of Moments estimation
- United 8 site adjustment methods
- Efficient internal looping for methods of moments approach
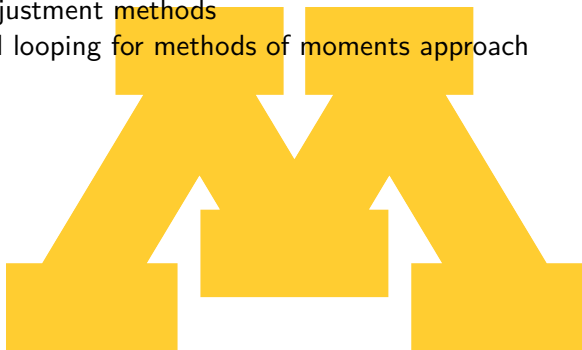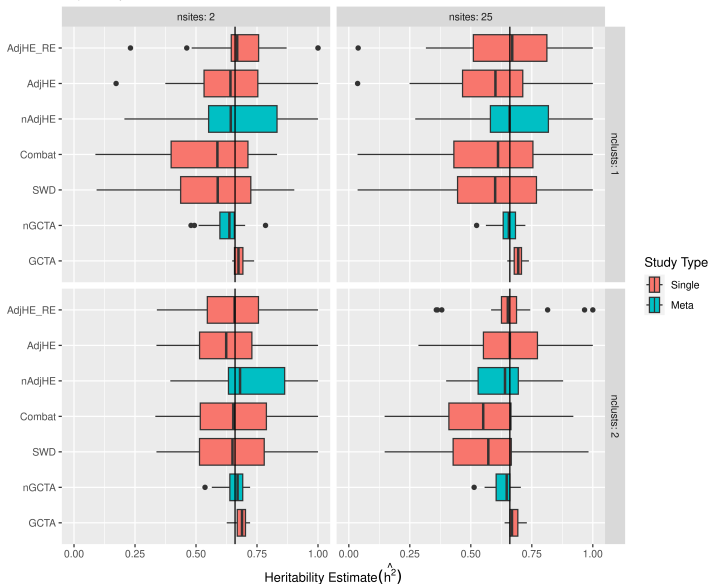
Thank you

Questions?

Estimation with balanced sites

Figure 9: Simulated comparisons

All ABCD estimates
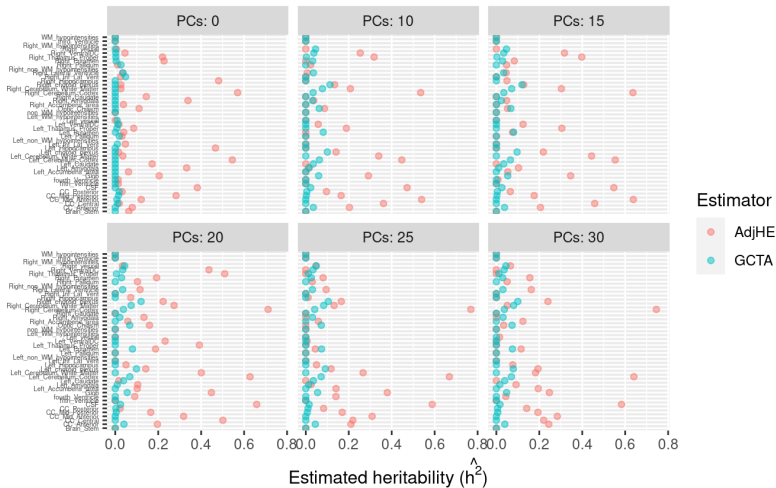
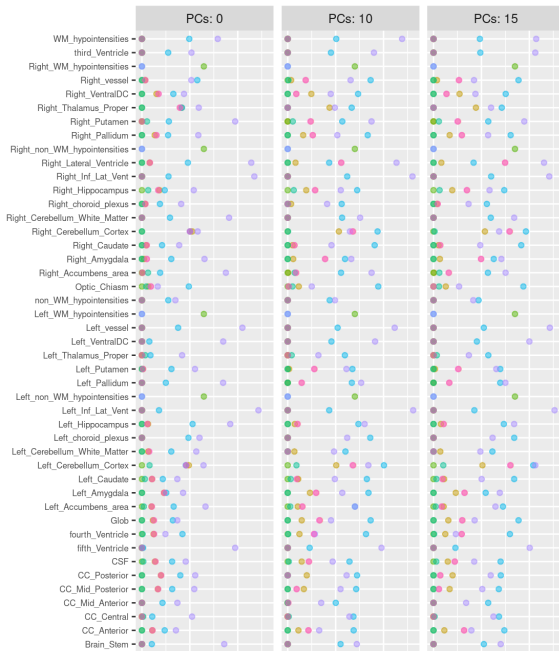Estimated heritability ($\hat{h}^2$)

Estimator
- AdjHE
- AdjHE_RE
- Combat
- GCTA
- nAdjHE
- nGCTA
- SWD

ABCD PCs

Site 16

European estimates

GxEMM

$$Y = X\alpha + G\beta + \sum GZ_k\gamma_k + Z_k\delta_k + \epsilon$$

▶ Simulating phenotypes conserving hertiability for ancestries

▶ Shared genetic effects

▶ Ancestry genetic effects

▶ Ancestry effects

▶ Assume effects proportional to frequency $\beta \sim N(0, \tau^2 \frac{\sigma^2}{m})$
$\tau_s^2 \propto f_s(1-f_s)^\alpha$

References

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2. Shepherd, A. M., Laurens, K. R., Matheson, S. L., Carr, V. J. & Green, M. J. Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. *Neurosci Biobehav Rev* **36**, 1342–1356 (2012).

3. Holzschneider, K. & Mulert, C. Neuroimaging in anxiety disorders. *Dialogues Clin Neurosci* **13**, 453–461 (2011).

4. Zhao, B. *et al.* Heritability of regional brain volumes in large-scale neuroimaging and genetic studies. *Cereb Cortex* **29**, 2904–2914 (2019).

5. Smit, D. J. A. *et al.* Heritability of head size in dutch and australian twin families at ages 0-50 years. *Twin Res Hum Genet* **13**, 370–380 (2010).