

Heritability of subcortical volumes in the adolescent brain

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Driven to DiscoverSM

Introduction and Objectives

Clinically diagnosed psychological disorders are associated with heritable regional subcortical brain volumes (rSBVs) in adults [2, 4]. To see if the same regions are heritable in adolescents, we analyzed rSBVs in the Adolescent Brain Cognitive Development study (ABCD) which has 10,000+ structural fMRI scans. Estimating Imaging derived phenotypes taken across multiple sites is complicated by confounding differences between sites [1]. In addition, sites have different distributions of subjects with respect to their genetic ancestries. Currently, no method of moments (MOM) estimator accounts for both influences which is important to get unbiased estimates.

Methods

- AdjHE is closed form solution to 2nd moment [3]

$$EY^* = X_C\beta_C + X_G\beta_G + X_S\beta_S \quad (1st \text{ Moment})$$

$$Y = Q_c Y = Y - X_C\hat{\beta}_C \quad (Residualize)$$

$$YY' = A\sigma_G^2 + S\sigma_S^2 + I\sigma_E^2 \quad (2nd \text{ Moment})$$

- Compared to existing methods for site effects theoretically and via simulations see (Figure 2)

$$E\hat{h}^2 = \frac{tr(A - I)T(EYY)T}{tr(A - I)T}$$

- Estimated on rSBV's in ABCD (see Figure 1)

Existing methods compared

- Site wise de-meaning

$$T := Q_s$$

- Adjusted residual adjustment

$$T := Q_{C,S}$$

- Combat

$$T = T_1 T_2$$

$$T_2 \xrightarrow{P} Q_S$$

$$T_1 \xrightarrow{P} I$$

- Covbat- Same as Combat followed by additional transformation

rSBV Heritability

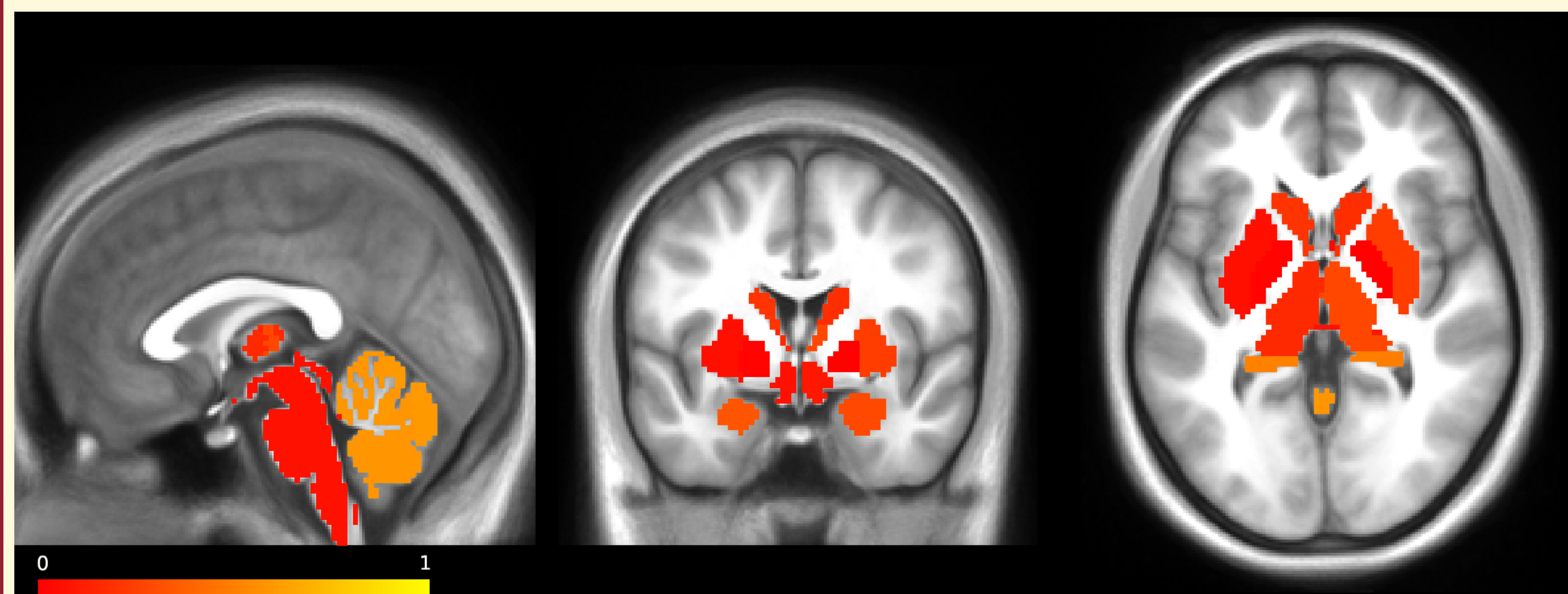


Figure 1: Heritability of rSBVs visualized on the Conte brain template. Yellow indicates high heritability, red indicates low.

Simulations

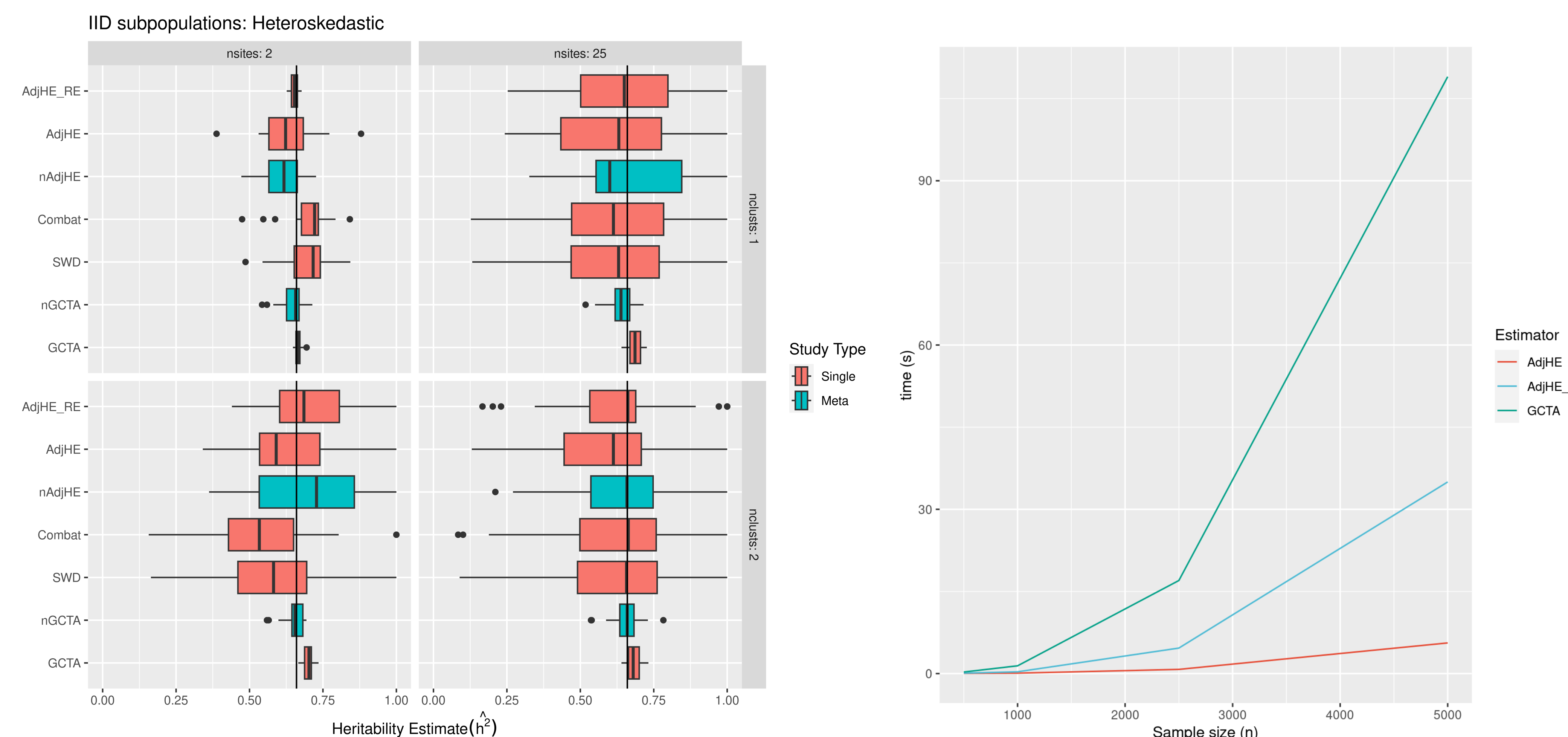


Figure 2: (Left) Simulation estimates under 2 and 25 sites (left and right columns) and 1 and 2 genetic ancestries (top and bottom rows). Estimates are compared between the proposed method "AdjHE_RE" and multiple other methods including GCTA. (Right) Time for analysis for multiple sample sizes for AdjHE (blue), AdjHE with random site effect (light blue), and GCTA (red).

Discussion

The new estimator **broadens unbiased estimation** to conditions where genetic ancestries and site effects vary between sites. We've shown the new estimator is unbiasedness theoretically and through simulations while providing at least **3x speed up** in estimation. In addition, we found **multiple regions with significant heritability** in the adolescent brain. We next hope to extend this method to multivariate traits.

ABCD Demographics

Characteristic	N = 11,878 [†]	Characteristic	N = 11,878 [†]
Household.Income		Race	
<50k	3,224 (27%)	Asian	252 (2.1%)
>=50k<100k	3,071 (26%)	Black	1,784 (15%)
100k+	4,565 (38%)	Hispanic	2,411 (20%)
Unknown	1,018 (8.6%)	Other	1,247 (10%)
Female	5,862 (49%)	Unknown	2 (<0.1%)
[†] n (%)		White	6,182 (52%)
		[†] n (%)	

Figure 3: Descriptions of key demographic variables in the ABCD dataset.

References

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