Multidimensional heritability analysis of neuroanatomical shape

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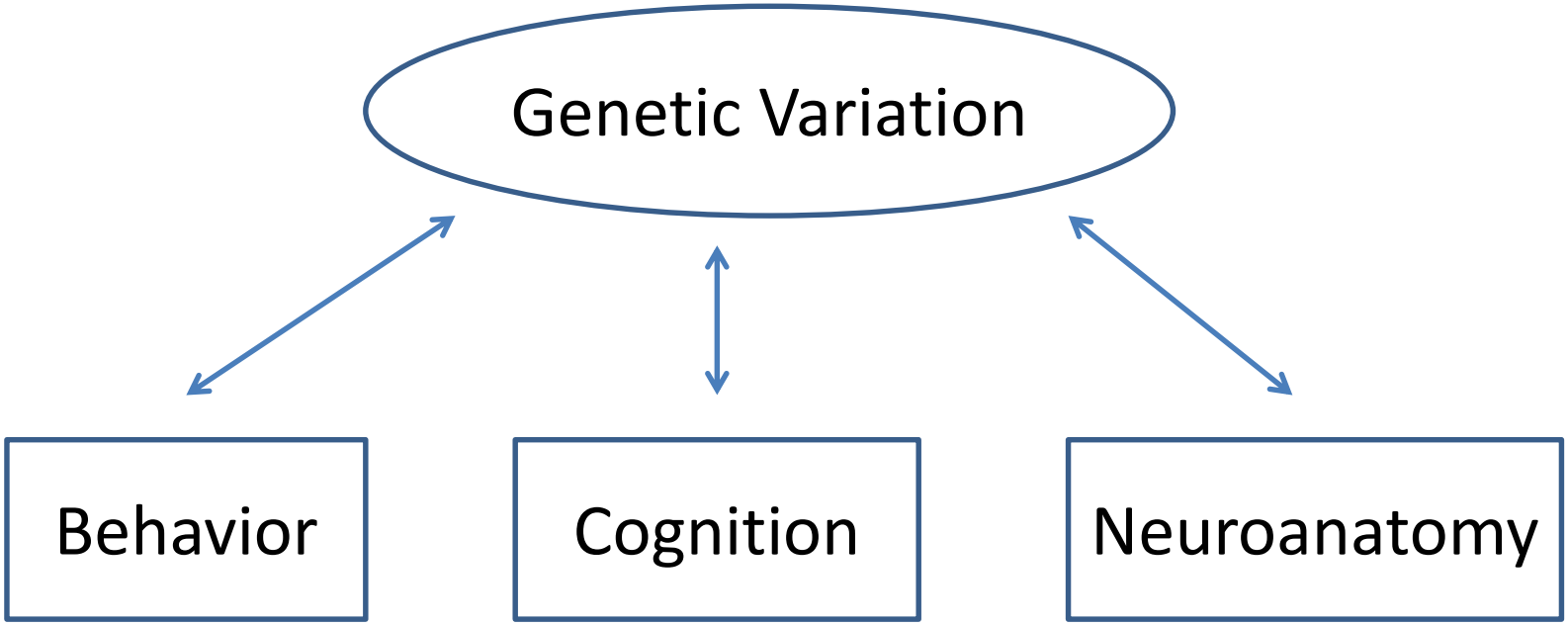
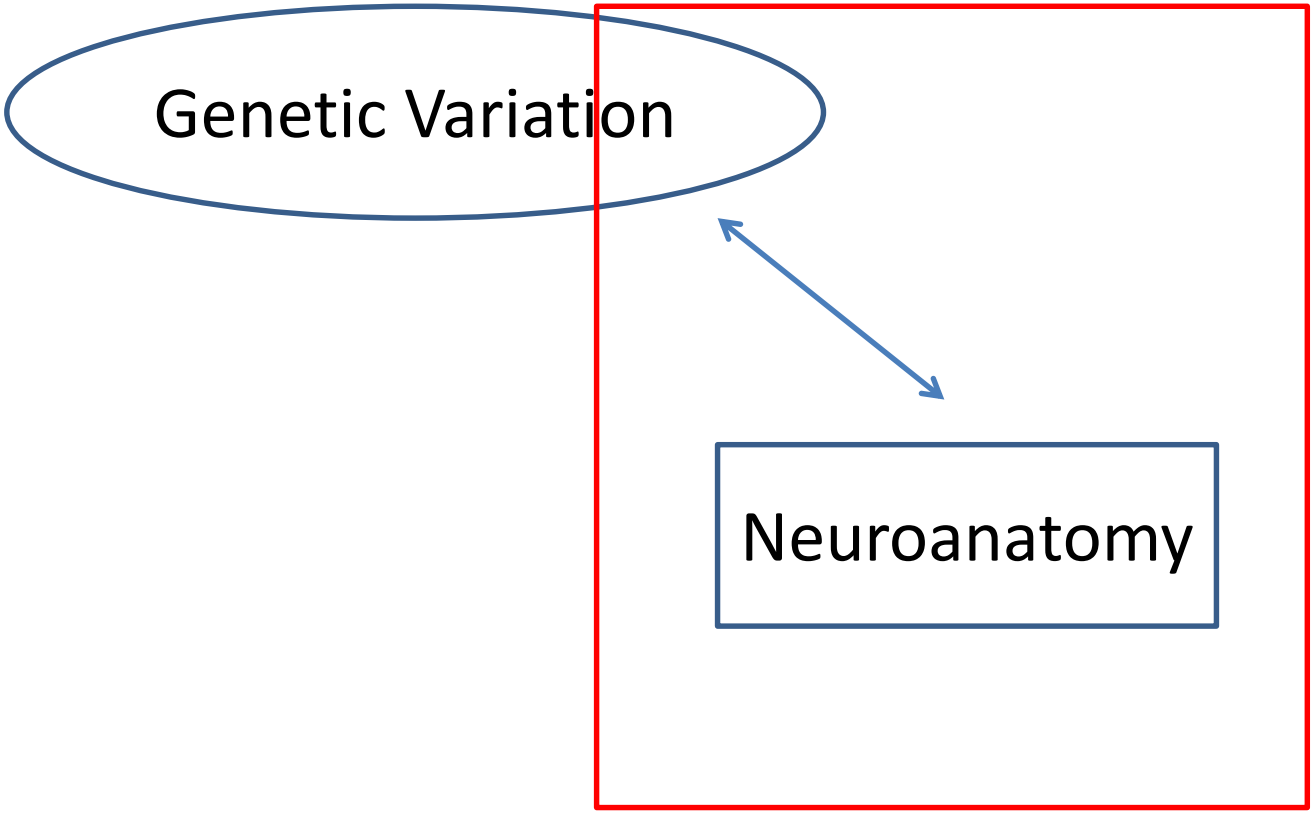
Brain Imaging Genetics

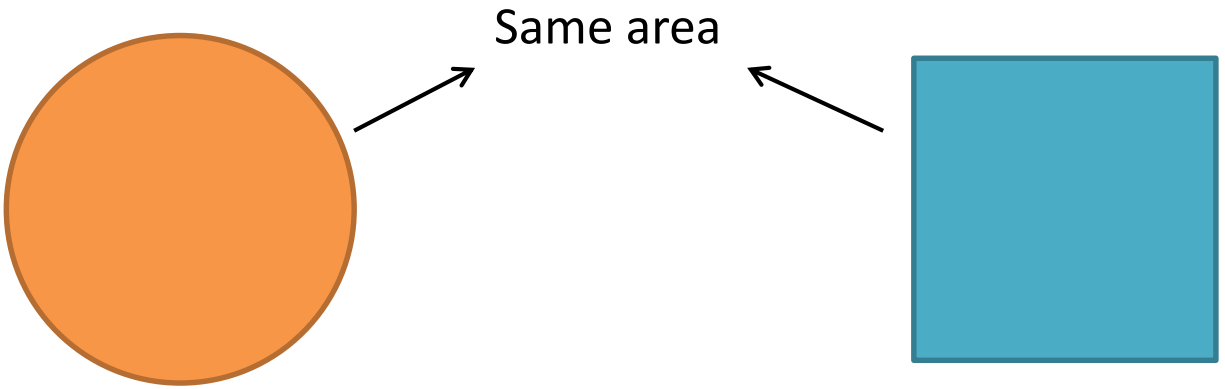


Brain Imaging Genetics



Descriptors of Brain Structures

- One-dimensional descriptors (Hibar2015; Stein2012; Sabuncu2012)
  - Volume
  - Surface area
  - …
- Drawbacks
  - Limited when capturing the anatomical variation



Descriptors of Brain Structures

- Multi-dimensional shape descriptor: truncated Laplace-Beltrami Spectrum (LBS)
  - $\psi: \mathrm{R}^n \to \mathrm{R}^{n+k}$ is the local parametrization of a submonifold M of R^{n+k}

    $g_{ij} =< \partial_i\psi, \partial_j\psi >, \;\; G = \left(g_{ij}\right)_{n\times n}, \;\; W = \sqrt{\det G}, \;\; g^{ij} = G^{-1}(i,j)$

  - If f and ϕ are real-valued functions defined on M, then

    $\nabla(f,\phi) = \sum_{i,j} g^{i,j}\, \partial_i f\, \partial_j \phi, \quad \Delta f = \frac{1}{W}\sum_{i,j} \partial_i\left(g^{ij} W\, \partial_j f\right)$

    where $\nabla(f,\phi) :=< \mathrm{grad}\, f,\ \mathrm{grad}\, \phi >$ and $\Delta f := \mathrm{div}(\mathrm{grad}\, f)$.

    Nabla operator — Laplace-Beltrami operator

  - Solve Laplacian eigenvalue problem: $\Delta f = \lambda f$

    eigenfunction — eigenvalue

Descriptors of Brain Structures

- Multi-dimensional shape descriptor: truncated Laplace-Beltrami Spectrum (LBS)

Translate Laplacian eigenvalue problem: $\Delta f = \lambda f$ to a variational problem:

- $\iint \phi \Delta f \, d\sigma = -\iint \nabla(f, \phi) \, d\sigma$ ← Green formula

- Since $\nabla(f, \phi) = \sum_{i,j} g^{i,j} \, \partial_i f \, \partial_j \phi$ and $\iint \phi \Delta f \, d\sigma = \iint \phi \, \lambda f \, d\sigma = -\lambda \iint \phi f d\sigma$
  $\Leftrightarrow \iint \sum_{i,j} g^{i,j} \, \partial_i f \, \partial_j \phi \, d\sigma = \lambda \iint \phi f d\sigma$

↖ variational problem

Descriptors of Brain Structures

- Multi-dimensional shape descriptor: truncated Laplace-Beltrami Spectrum (LBS)

Discretization of $\iint \sum_{i,j} g^{i,j}\, \partial_i f\, \partial_j \phi\; d\sigma = \lambda \iint \phi f d\sigma$:

- Choose n linearly independent form functions: $\phi_1(\vec{x}), \phi_2(\vec{x}), \ldots, \phi_n(\vec{x})$ as basis functions (e.g. $x, x^2, x^3, \ldots$) defined on the parameter space.

- Any eigenfunction f can be approximately projected to the basis functions:
  $f(\vec{x}) \approx F(\vec{x}) = U_1\phi_1(\vec{x}) + \cdots + U_n\phi_n(\vec{x})$

- To solve $U_{(\cdot)}$, substitute f and $\phi_{(\cdot)}$ into the variational problem.

- Define $A = (a_{lm})_{n\times n} = \left(\iint \left(\sum_{j,k} (\partial_j F_l)(\partial_k F_m) g^{jk} d\sigma\right)\right)_{n\times n}$ and $B = (b_{lm})_{n\times n} = \left(\iint F_l F_m d\sigma\right)_{n\times n}$
  => $AU = \lambda BU$ ← General eigenvalue problem

Descriptors of Brain Structures

- Multi-dimensional shape descriptor: truncated Laplace-Beltrami Spectrum (LBS)
  - Solve a Laplacian eigenvalue problem defined based on the brain region
  - Obtain the first M eigenvalues
- Properties (Reuter 2006):
  - Isometric invariant

- **For planar shapes and 3D-solids:**

isometry ⇔ congruency
(identical after rigid body transformation)

- For surface:

isometry ≠ congruency

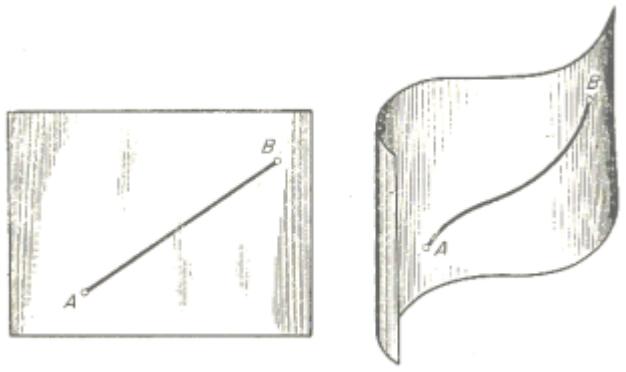


Fig. 2

Descriptors of Brain Structures

- Multi-dimensional shape descriptor: truncated Laplace-Beltrami Spectrum (LBS)
  - Solve a Laplacian eigenvalue problem defined based on the brain region
  - Obtain the first M eigenvalues
- Properties (Reuter 2006):
  - Isometric invariant
  - scaling a n-dimensional manifold by the factor a results in scaled eigenvalues by the factor $\frac{1}{a^2}$
  - …

In this paper, eigenvalues are scaled:

$$\tilde{\tilde{\lambda}}_{i,m} = \tilde{\lambda}_{i,m} \cdot V_i^{\ 2/3}$$

i: subject; m: dimension

Heritability

- A phenotype/trait can be influenced by genetic and environmental effects.

- Heritability: how much of the variation in a phenotype/trait is due to variation in genetic factors.

Main Idea of This Paper

- Truncated LBS is more representative for a shape compared to volume.
- Use truncated LBS as descriptors for 12 brain regions to compute heritability. Compare that with volume-based heritability.
- To adapt truncated LBS into GCTA (Genome-wide Complex Trait Analysis) (Yang 2011) heritability model, propose a multi-dimensional heritability model.

GCTA heritability model

$N \times 1$ trait vector
(N: #subjects)

$$y = g + c + e$$

$$g \sim N(0, \sigma_A^2 K) \qquad c \sim N(0, \sigma_C^2 \Lambda) \qquad e \sim N(0, \sigma_E^2 I)$$

Additive genetic component

Common environmental component

Unique environmental component

GCTA heritability model

$$y = g + c + e$$

$$g \sim N(0, \sigma_A^2 K) \qquad c \sim N(0, \sigma_C^2 \Lambda) \qquad e \sim N(0, \sigma_E^2 I)$$

K: genetic similarity matrix

- Familial study: $K = 2 \times Kinship\ Coefficients$.
  E.g. parent-offspring (0.5), identical twins (1), full siblings (0.5), half siblings (0.25)

- Unrelated subjects study: genome-side single-nucleotide polymorphism (SNP) data

GCTA heritability model

$$y = g + c + e$$

$$g \sim N(0, \sigma_A^2 K) \qquad c \sim N(0, \sigma_C^2 \Lambda) \qquad e \sim N(0, \sigma_E^2 I)$$

What is Single-Nucleotide Polymorphism (SNP):

- Each locus on a DNA sequence is a single nucleotide adenine (A), thymine (T), cytosine (C), or guanine (G).
- SNP: a DNA sequence variation occurring when the types of single nucleotide in the genome (or other shared sequence) differs between individuals or paired chromosomes in one subject. E.g., AAGC**C**TA and AAGC**T**TA.
- SNP can leads to alleles (variants of a given gene).
- Each SNP can have 3 genotypes: AA, Aa, aa (denoted as 0-2)

GCTA heritability model

$$y = g + c + e$$

$$g \sim N(0, \sigma_A^2 K) \qquad c \sim N(0, \sigma_C^2 \Lambda) \qquad e \sim N(0, \sigma_E^2 I)$$

How to compute genetic similarity from SNP:

- X(#subjects x #SNPs). $\longrightarrow \begin{bmatrix} 0 & \cdots & 2 \\ 2 & \cdots & 1 \\ \vdots & & \vdots \\ 1 & \cdots & 0 \end{bmatrix}$
- Standardize each column of X (mean 0, variance 1).
- $K = \frac{XX^T}{\#SNPs}$

GCTA heritability model

$$y = g + c + e$$

$$g \sim N(0, \sigma_A^2 K) \qquad c \sim N(0, \sigma_C^2 \Lambda) \qquad e \sim N(0, \sigma_E^2 I)$$

Λ: shared environment matrix between the subjects

- Familial study: e.g., twins & non-twin siblings (1)
- Unrelated subjects study: Λ vanishes

GCTA heritability model

$$y = g + c + e$$

$$g \sim N(0, \sigma_A^2 K) \qquad c \sim N(0, \sigma_C^2 \Lambda) \qquad e \sim N(0, \sigma_E^2 I)$$

Identical matrix

GCTA heritability model

$$y = g + c + e$$

$$g \sim N(0, \sigma_A^2 K) \qquad c \sim N(0, \sigma_C^2 \Lambda) \qquad e \sim N(0, \sigma_E^2 I)$$

heritability → $$h^2 = \frac{\sigma_A^2}{\sigma_A^2 + \sigma_C^2 + \sigma_E^2}$$

h^2: the variance in the trait explained by the variance in additive genetic component

Multi-dimensional traits heritability model

$N \times M$ trait matrix
(N: #subjects)
(M: #dimensions)

$$Y = G + C + E$$

$$vec(G) \sim N\left(0, \Sigma_A \otimes K\right),\ vec(C) \sim N\left(0, \Sigma_C \otimes \Lambda\right),\ vec(E) \sim N\left(0, \Sigma_E \otimes I\right)$$

$\Sigma_A = \left(\sigma_{A_{rs}}\right)_{M \times M}$: $\sigma_{A_{rs}}$ is the genetic covariance between r-th and s-th dimensions in traits

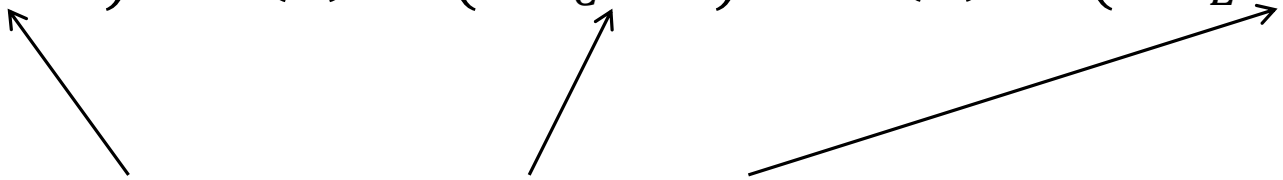
$\Sigma_C = \left(\sigma_{C_{rs}}\right)_{M \times M}$: $\sigma_{C_{rs}}$ is the common environmental covariance between r-th and s-th dimensions in traits

$\Sigma_E = \left(\sigma_{E_{rs}}\right)_{M \times M}$: $\sigma_{E_{rs}}$ is the unique environmental covariance between r-th and s-th dimensions in traits

Multi-dimensional traits heritability model

$$Y = G + C + E$$

$$vec(G) \sim N\left(0, \Sigma_A \otimes K\right),\ vec(C) \sim N\left(0, \Sigma_C \otimes \Lambda\right),\ \ vec(E) \sim N\left(0, \Sigma_E \otimes I\right)$$



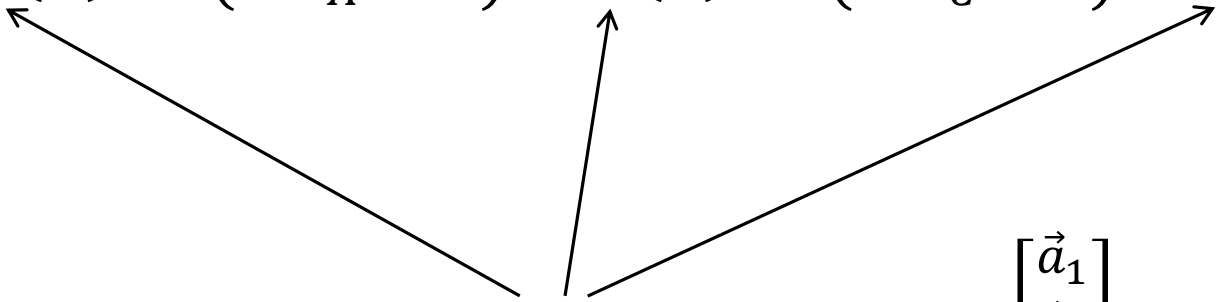
⊗: Kronecker product

$$\Sigma_{A_{rs}} \otimes K = \begin{bmatrix} \sigma_{A_{11}} K & \sigma_{A_{12}} K & \cdots & \sigma_{A_{1M}} K \\ \sigma_{A_{21}} K & \sigma_{A_{22}} K & \cdots & \sigma_{A_{2M} K} \\ \vdots & \vdots & & \vdots \\ \sigma_{A_{M1}} K & \sigma_{A_{M2}} K & \cdots & \sigma_{A_{MM}} K \end{bmatrix}$$

Multi-dimensional traits heritability model

$$Y = G + C + E$$

$$vec(G) \sim N\left(0, \Sigma_A \otimes K\right),\ vec(C) \sim N\left(0, \Sigma_C \otimes \Lambda\right),\ vec(E) \sim N\left(0, \Sigma_E \otimes I\right)$$



$$vec([\vec{a}_1, \vec{a}_2, \cdots, \vec{a}_k]) = \begin{bmatrix} \vec{a}_1 \\ \vec{a}_2 \\ \vdots \\ \vec{a}_k \end{bmatrix}$$

Multi-dimensional traits heritability model

$$Y = G + C + E$$

$$vec(G) \sim N\left(0, \Sigma_A \otimes K\right),\ vec(C) \sim N\left(0, \Sigma_C \otimes \Lambda\right),\ \ vec(E) \sim N\left(0, \Sigma_E \otimes I\right)$$

heritability

$$h^2 = \frac{\mathrm{tr}(\Sigma_A)}{\mathrm{tr}(\Sigma_A) + \mathrm{tr}(\Sigma_C) + \mathrm{tr}(\Sigma_E)} = \sum_{m=1}^{M} \gamma_m h_m^2$$

where

$$\gamma_m = \frac{\sigma_{A_{mm}} + \sigma_{C_{mm}} + \sigma_{E_{mm}}}{\sum_{p=1}^{M}\left(\sigma_{A_{pp}} + \sigma_{C_{pp}} + \sigma_{E_{pp}}\right)}$$

$$h_m^2 = \frac{\sigma_{A_{mm}}}{\sigma_{A_{mm}} + \sigma_{C_{mm}} + \sigma_{E_{mm}}}$$

The multi-dimensional trait heritability is a weighted average of the heritability of each dimension.

Multi-dimensional traits heritability model

- Properties
  - Invariant to rotations of data

$$Y = G + C + E \quad (1)$$

$$YT = GT + CT + ET \quad (2)$$

$$T^T T = T T^T = I$$

$$h_T^2 = h^2$$

heritability from model (2)

heritability from model (1)

Consider covariates

- Sometimes, we want to study the effects after controlling some nuisance variables by regressing them out.
- E.g., age, gender, handness

Consider covariates

Covariates ($N \times q$)

$$Y = XB + G + C + E$$

$$vec(G) \sim N\left(0, \Sigma_A \otimes K\right),\ vec(C) \sim N\left(0, \Sigma_C \otimes \Lambda\right),\ \ vec(E) \sim N\left(0, \Sigma_E \otimes I\right)$$

U: $N \times (N - q)$

$$U^T X = 0$$
$$U^T U = I$$
$$UU^T = I - X(X^T X)^{-1} X^T$$

$$\tilde{Y} = U^T Y = U^T G + U^T C + U^T E = \tilde{G} + \tilde{C} + \tilde{E}$$

$$vec\left(\tilde{G}\right) \sim N\left(0, \Sigma_A \otimes (U^T K U)\right),\quad vec\left(\tilde{C}\right) \sim N\left(0, \Sigma_C \otimes (U^T \Lambda U)\right),$$

$$vec\left(\tilde{E}\right) \sim N\left(0, \Sigma_E \otimes I\right)$$

Analysis

- Datasets:
  - Genomics Superstruct Project (GSP; N = 1320) – unrelated subjects
  - Human Connectome Project (HCP; N = 590)
    - 72 monozygotic twin pairs
    - 69 dizygotic twin pairs
    - 253 full siblings of twins
    - 55 singletons
- 12 brain structures
- Traits
  - Volume
  - Truncated LBS

Volume heritability (GSP data)

Table 1 | SNP heritability estimates $\hat{h}^2_{SNP}$ of the volume of brain structures using the GSP sample.

Structure	$\hat{h}^2_{SNP}$	s.e.	Wald *P* value	Perm *P* value	Reliability
Accumbens area	0.001	0.281	0.500	1.000	0.797
Amygdala	0.141	0.281	0.308	0.305	0.864
Caudate	**0.657**	0.281	0.010	0.009	0.947
Cerebellum	0.084	0.281	0.383	0.382	0.989
Corpus callosum	**0.538**	0.281	0.028	0.029	0.882
Hippocampus	0.005	0.281	0.493	0.492	0.939
Lateral Ventricle	0.331	0.281	0.119	0.120	0.995
Third ventricle	**0.500**	0.281	0.038	0.040	0.832
Fourth ventricle	0.381	0.281	0.087	0.089	0.986
Pallidum	0.300	0.281	0.142	0.142	0.642
Putamen	0.328	0.281	0.121	0.122	0.934
Thalamus	0.252	0.281	0.184	0.186	0.867

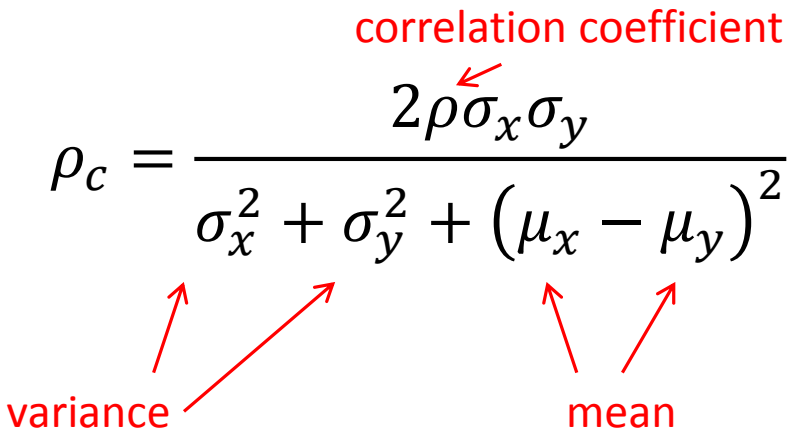
GSP, Genomics Superstruct Project; SNP, single-nucleotide polymorphism.
The s.e.'s were computed using an approximation, which, given the empirical genetic similarity matrix, only depends on the sample size. *P* values were obtained by the Wald test and permutation inference (based on 10,000 permutations), respectively. The strong agreement between the parametric and nonparametric *P* values indicates that the estimated s.e. values are accurate. Estimates with uncorrected significant *P* values (<0.05) are shown in bold. Test-retest reliability of the volumetric measurements was computed as Lin's concordance correlation coefficient using measurements from 42 subjects with repeated scans on separate days.

- Before multiple comparisons correction: 3/12 brain structures are significant
- After multiple comparisons correction: none is significant
- Most structures: parametric & nonparametric p values are similar => standard errors estimates are accurate

Volume heritability (GSP data)

Test-retest reliability:

- Lin's concordance correlation coefficient



x, y: use repeated runs on separate days of the same set of subjects

Truncated LBS heritability (GSP data)

Table 2 | SNP heritability estimates $\hat{h}^2_{SNP}$ of the shape of brain structures using the GSP sample.

Structure	$\hat{h}^2_{SNP}$	s.e.	Wald *P* value	Perm *P* value	Reliability
Accumbens area	**0.237**	0.135	0.039	0.039	0.418
Amygdala	0.061	0.139	0.330	0.327	0.670
Caudate	***0.499***	0.188	0.004	0.005	0.759
Cerebellum	***0.452***	0.192	0.009	0.009	0.844
Corpus Callosum	***0.264***	0.133	0.023	0.022	0.622
Hippocampus	***0.347***	0.169	0.020	0.019	0.866
Lateral Ventricle	0.190	0.153	0.107	0.105	0.890
Third ventricle	***0.500***	0.157	0.001	0.001	0.761
Fourth ventricle	0.005	0.208	0.490	0.491	0.633
Pallidum	0.061	0.117	0.299	0.299	0.402
Putamen	***0.413***	0.148	0.003	0.003	0.781
Thalamus Proper	0.086	0.143	0.274	0.276	0.552

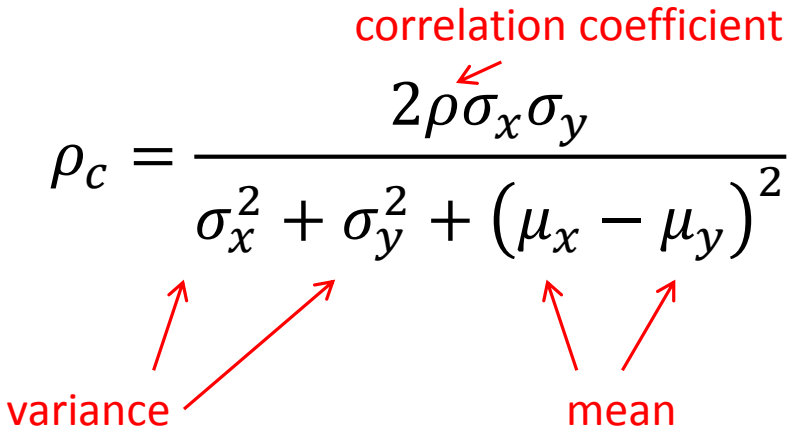
GSP, Genomics Superstruct Project; SNP, single-nucleotide polymorphism.
S.e.'s are less than those corresponding to volume heritability. *P* values were obtained by the Wald test and permutation inference (based on 10,000 permutations), respectively. The strong agreement between the parametric and nonparametric *P* values indicates that the s.e. estimates are accurate. Estimates with uncorrected significant *P* values (<0.05) are shown in bold. False discovery rate - corrected significant *P* values (<0.05) are shown in italics. Test-retest reliability of the shape measurements were computed as the average Lin's concordance correlation coefficient of individual components of the LBS-based shape descriptor from 42 subjects with repeated scans on separate days.

- Before multiple comparisons correction: 7/12 brain structures are significant
- After multiple comparisons correction: 5/12 brain structures are significant
- Most structures: parametric & nonparametric p values are similar => standard errors estimates are accurate
- Smaller standard error than volume-based heritability

Truncated LBS heritability (GSP data)

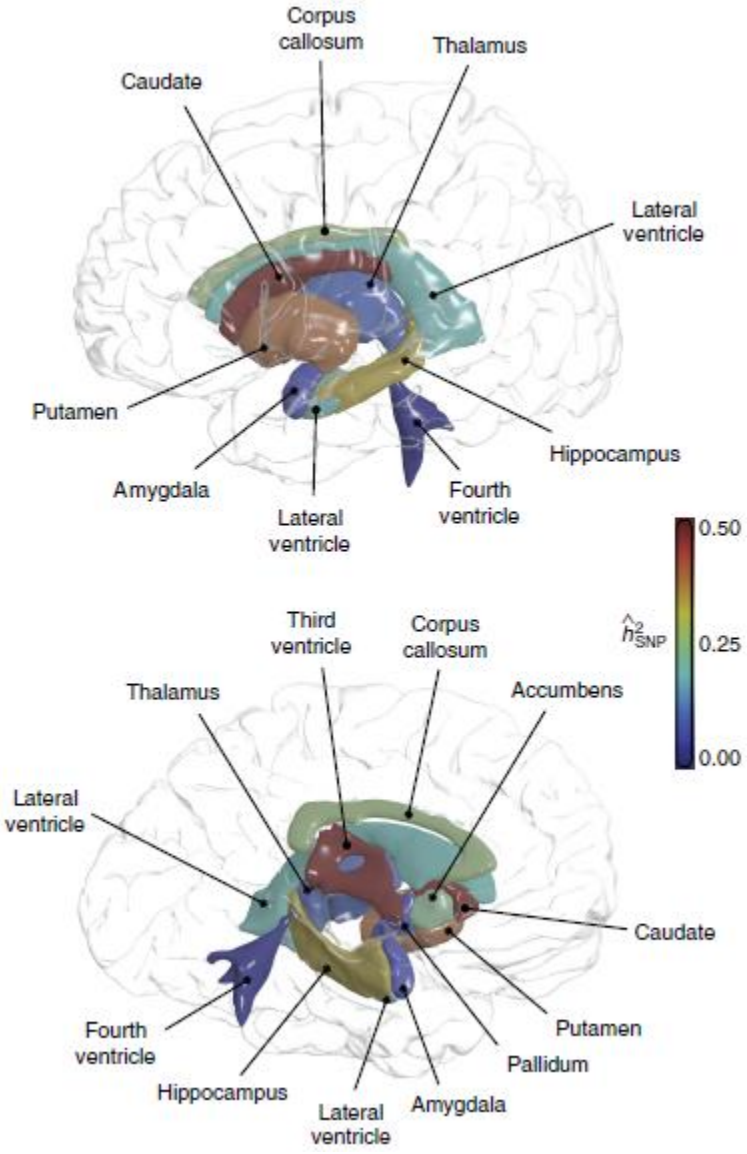
Test-retest reliability:

- Averaged Lin's concordance correlation coefficient across M dimensions



x, y: use repeated runs on separate days of the same set of subjects

Truncated LBS heritability (GSP data)



Truncated LBS heritability (HCP data)

Structure	$\widehat{h}^2$	Standard Error
Accumbens area	0.309	0.162
Caudate	0.583	0.124
Cerebellum	0.653	0.120
Corpus Callosum	0.558	0.136
Hippocampus	0.363	0.190
Third Ventricle	0.536	0.134
Putamen	0.483	0.212

- Only significant brain structures results are shown
- Consistently higher than GSP dataset
  - Possible reason: in unrelated subjects only the variation of some common SNPs are captured.

Visualizing principal mode of shape variation

- PCA is a kind of rotation of data. The first PC of LBS explains a large percentage of shape variation.

- Heritability model: (1) invariant to rotation; (2) heritability of multi-dimensional trait = weighted average of each dimension's heritability

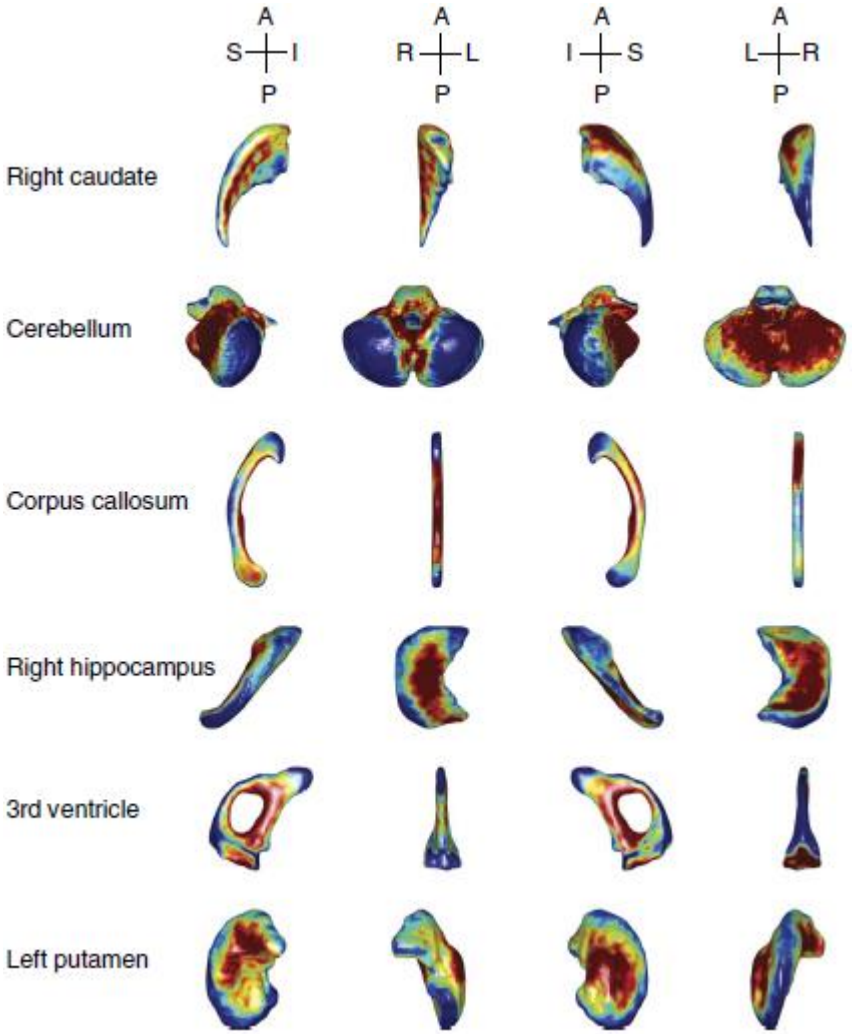
- The heritability of truncated LBS is the weighted average of the first M PCs' heritability.

Visualizing principal mode of shape variation

Procedures (for one brain structure)

1. Register each subject's mask (1 – in structure, 0 – out of structure) to a common used template.
2. Create a population average of structure surface for plotting
   - A weighted average of all subjects' registered mask image
   - Weight: Gaussian kernel
     - center: average of first PC
     - distance: subject-specific corresponding first PC <-> center
     - Width: resulting 500 shapes have non-0 weights
   - The isosurface with 0.5 in the averaged map
3. Use the same Gaussian kernel, generate averaged maps by including the shapes around +2 standard deviation of the first PC (-2 s.d. as well)
4. Plot the difference between the two maps in step 3 on the surface generated in step 2.

Visualizing principal mode of shape variation



Red: shapes around +2 s.d. are larger than -2 s.d.

Blue: shapes around -2 s.d. are larger than +2 s.d.

Strengths

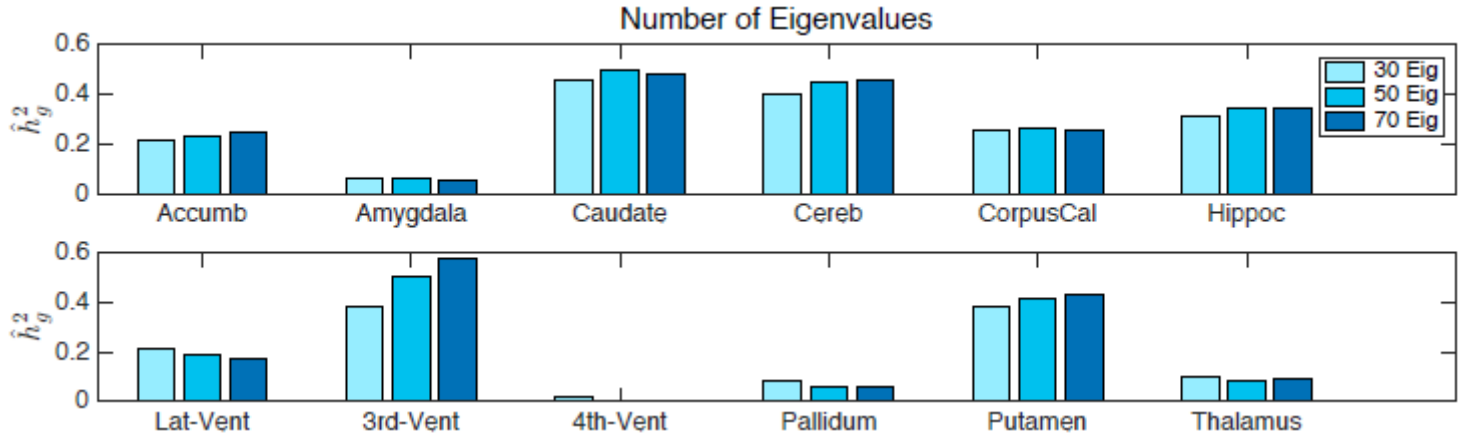
- Use truncated LBS instead of volume as features
  - Capture more shape variation
  - Isometry invariance
  - Does not require any registration or mapping (Reuter 2006 & 2009)
- Generalize the concept of heritability into multi-dimensional phenotypes
  - Other applications (multi-tests of one behavior; disease study)

Strengths

- Variability of heritability estimation
  - Multi-dimensional trait heritability model < original GCTA model (unrelated subject dataset)
  - Heritability estimates are more accurate, more significant
- Propose a visualization method for shape variation
  - Interpretation: shape variation along the first PC axis of the shape descriptor

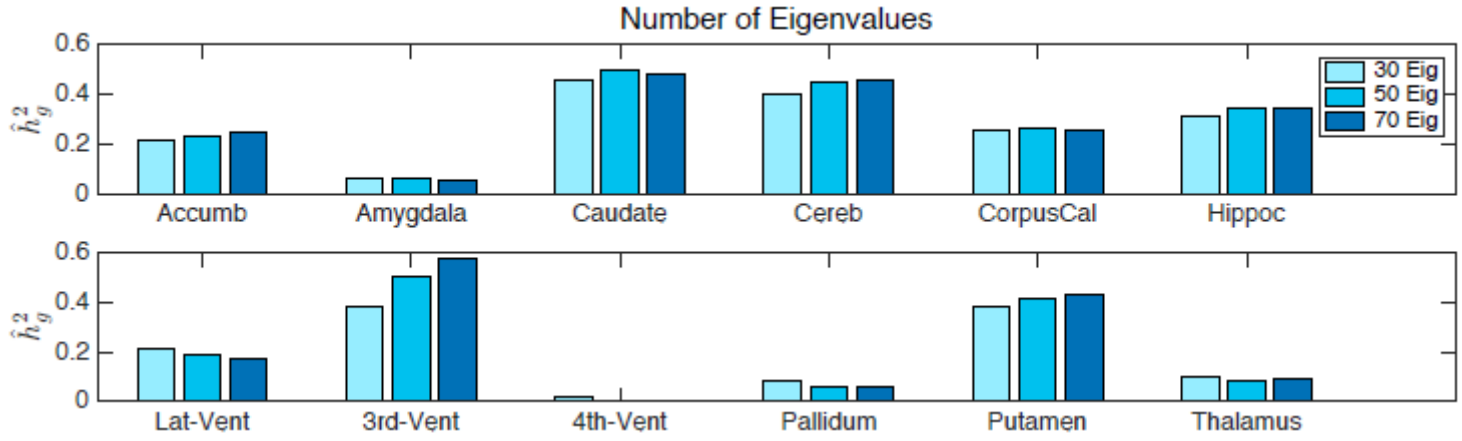
Weakness

- Optimal number of eigenvalue may not be 50
  - Only 30, 50, 70 are tested
  - Error bars for difference number of eigenvalues are not shown
  - Other number except 50 (used in paper) could lead to higher heritability and smaller error bars



Weakness

- Optimal number of eigenvalue can be different for different brain structures
  - Amygdala: heritability is similar for 30, 50, 70 eigenvalues (even decrease)
  - 3rd-ventricle: heritability increases from 0.4 to 0.6



Weakness

- Links between proposed visualization method and LBS heritability are not clear.

- Only volume-based GCTA heritability is compared to the new method and new model.
  - More comparisons with the literature (e.g., Gilmore 2010; Baare 2001)

Backup: invariant to rotations of data

$$cov\big(vec(GT)\big)$$
$$= cov\big((T^T \otimes I)vec(G)\big)$$
$$= (T^T \otimes I)vec(G)(T \otimes I)$$
$$= (T^T \otimes I)(\Sigma_A \otimes K)(T \otimes I)$$
$$= (T^T \Sigma_A T) \otimes K$$

Theorem: $vec(AXB) = (B^T \otimes A)vec(X)$
Here $A = I, X = G, B = T$

- $(A \otimes B)^T = A^T \otimes B^T$
- $cov(AX) = Acov(X)A^T$

$(A \otimes B)(C \otimes D) = AC \otimes BD$

Similarly, $cov\big(vec(CT)\big) = (T^T \Sigma_C T) \otimes \Lambda$, $cov\big(vec(ET)\big) = (T^T \Sigma_E T) \otimes I$

$$h_T^2 = \frac{tr[T^T \Sigma_A T]}{tr[T^T \Sigma_A T] + tr[T^T \Sigma_C T] + tr[T^T \Sigma_E T]}$$
$$= \frac{tr[\Sigma_A (TT^T)]}{tr[\Sigma_A (TT^T)] + tr[\Sigma_C (TT^T)] + tr[\Sigma_E (TT^T)]}$$
$$= \frac{tr[\Sigma_A]}{tr[\Sigma_A] + tr[\Sigma_C] + tr[\Sigma_E]} = h^2$$

- $tr[ABC] = tr[BCA] = tr[CAB]$
- Associative property of matrix multiplication

Backup: multi-dimensional trait heritability is a weighted average of heritability of each dimension

$$h^2 = \frac{tr[\Sigma_A]}{tr[\Sigma_A + \Sigma_C + \Sigma_E]}$$

$$= \frac{\sum_{m=1}^{M} \sigma_{A_{mm}}}{\sum_{p=1}^{M} \sigma_{A_{pp}} + \sum_{p=1}^{M} \sigma_{C_{pp}} + \sum_{p=1}^{M} \sigma_{E_{pp}}}$$

$$= \sum_{m=1}^{M} \frac{\sigma_{A_{mm}} + \sigma_{C_{mm}} + \sigma_{E_{mm}}}{\sum_{p=1}^{M} \left(\sigma_{A_{pp}} + \sigma_{C_{pp}} + \sigma_{E_{pp}}\right)} \cdot \frac{\sigma_{A_{mm}}}{\sigma_{A_{mm}} + \sigma_{C_{mm}} + \sigma_{E_{mm}}}$$

$$= \sum_{m=1}^{M} \gamma_m h_m^2$$

Backup: moment-matching estimator for unrelated subjects (no shared environmental component)

$$cov[y_r, y_s] = \sigma_{A_{rs}} K + \sigma_{E_{rs}} I \quad \Longrightarrow \quad y_r y_s^T = \sigma_{A_{rs}} K + \sigma_{E_{rs}} I$$

To estimate $\sigma_{A_{rs}}$, $\sigma_{E_{rs}}$, use a regression model:

$$vec(y_r y_s^T) = \sigma_{A_{rs}} vec(K) + \sigma_{E_{rs}} vec(I)$$

$$\Longrightarrow \quad y_s \otimes y_r = \sigma_{A_{rs}} vec(K) + \sigma_{E_{rs}} vec(I)$$

$$\Longrightarrow \begin{cases} vec(K)^T (y_s \otimes y_r) = \sigma_{A_{rs}} vec(K)^T vec(K) + \sigma_{E_{rs}} vec(K)^T vec(I) \\ vec(I)^T (y_s \otimes y_r) = \sigma_{A_{rs}} vec(I)^T vec(K) + \sigma_{E_{rs}} vec(I)^T vec(I) \end{cases}$$

$$\Longrightarrow \begin{cases} (y_s \otimes y_r)^T vec(K) = \sigma_{A_{rs}} vec(K)^T vec(K) + \sigma_{E_{rs}} vec(I)^T vec(K) \\ (y_s \otimes y_r)^T vec(I) = \sigma_{A_{rs}} vec(K)^T vec(I) + \sigma_{E_{rs}} vec(I)^T vec(I) \end{cases}$$

$$\Longrightarrow \begin{cases} (y_s^T \otimes y_r^T) vec(K) = \sigma_{A_{rs}} vec(K)^T vec(K) + \sigma_{E_{rs}} vec(I)^T vec(K) \\ (y_s^T \otimes y_r^T) vec(I) = \sigma_{A_{rs}} vec(K)^T vec(I) + \sigma_{E_{rs}} vec(I)^T vec(I) \end{cases}$$

$$\Longrightarrow \begin{cases} y_r^T K y_s = \sigma_{A_{rs}} tr[K^2] + \sigma_{E_{rs}} tr[K] \\ y_r^T y_s = \sigma_{A_{rs}} tr[K] + \sigma_{E_{rs}} tr[I] \end{cases}$$

Backup: moment-matching estimator for unrelated subjects (no shared environmental component)

$$\Rightarrow \quad \begin{bmatrix} \sigma_{A_{rs}} \\ \sigma_{E_{rs}} \end{bmatrix} = \begin{bmatrix} tr[K^2] & tr[K] \\ tr[K] & tr[I] \end{bmatrix}^{-1} \begin{bmatrix} y_r^T K y_s \\ y_r^T y_s \end{bmatrix}$$

$$\Rightarrow \quad \begin{cases} \hat{\sigma}_{A_{rs}} = \dfrac{y_r^T (NK - tr[K]I) y_s}{N tr[K^2] - tr^2[K]} \coloneqq \dfrac{y_r^T (K - \tau I) y_s}{\nu_K} \\ \hat{\sigma}_{E_{rs}} = \dfrac{y_r^T (tr[K^2]I - tr[K]K) y_s}{N tr[K^2] - tr^2[K]} = \dfrac{y_r^T (\kappa I - \tau K) y_s}{\nu_K} \end{cases}$$

where $\tau = {}^{tr[K]}/_{N},\ \kappa = {}^{tr[K^2]}/_{N},\ \nu_K = tr[K^2] - {}^{tr^2[K]}/_{N} = N(\kappa - \tau)$

$$\Rightarrow \quad \hat{\Sigma}_A = \frac{Y^T (K - \tau I) Y}{\nu_K}, \qquad \hat{\Sigma}_E = \frac{Y^T (\kappa I - \tau K) Y}{\nu_K}$$

Backup: sampling variance of the point estimator

$$Q_A \coloneqq \frac{K - \tau I}{\nu_K}, \qquad Q_E \coloneqq \frac{\kappa I - \tau K}{\nu_K}$$

$$t_A \coloneqq tr\left[\hat{\Sigma}_A\right] = tr[Y^T Q_A Y], \qquad t_E = tr\left[\hat{\Sigma}_E\right] = tr[Y^T Q_E Y], \qquad t = \begin{pmatrix} t_A \\ t_E \end{pmatrix}$$

The heritability is a function of t: $f(t) = \frac{t_A}{t_A + t_E}$

$$var[h^2_{SNP}] = var[f(t)] \approx \frac{\partial f(t)}{\partial t} cov[t] \frac{\partial f(t)}{\partial t^T}$$

where $\frac{\partial f(t)}{\partial t} = \left(\frac{\partial f(t)}{\partial t}, \frac{\partial f(t)}{\partial t}\right) = \left(\frac{t_E}{(t_A + t_E)^2}, \frac{-t_A}{(t_A + t_E)^2}\right)$

Define $V_{rs} = cov[y_r, y_s] = \sigma_{A_{rs}} K + \sigma_{E_{rs}} I$

Backup: sampling variance of the point estimator

$$cov\{tr[Y^T Q_\alpha Y], tr[Y^T Q_\beta Y]\}$$

$$= \sum_{r,s=1}^{M} cov\{y_r^T Q_\alpha y_r, y_s^T Q_\beta y_s\}$$

Quadratic form of statistics:
$cov[\epsilon^T \Lambda_1 \epsilon, \epsilon^T \Lambda_2 \epsilon] = 2tr[\Lambda_1 \Sigma \Lambda_2 \Sigma] + 4\mu^T \Lambda_1 \Sigma \Lambda_2 \mu$
Here $\mu = 0$

$$= 2\sum_{r,s=1}^{M} tr[Q_\alpha V_{rs} Q_\beta V_{rs}]$$

$$V_{rs} = \sigma_{A_{rs}} K + \sigma_{E_{rs}} I \approx \sigma_{A_{rs}} I + \sigma_{E_{rs}} I$$

$$\Rightarrow \quad cov[t] = 2\sum_{r,s=1}^{M} \begin{bmatrix} tr[Q_A V_{rs} Q_A V_{rs}] & tr[Q_A V_{rs} Q_E V_{rs}] \\ tr[Q_E V_{rs} Q_A V_{rs}] & tr[Q_E V_{rs} Q_E V_{rs}] \end{bmatrix}$$

$$\approx 2\sum_{r,s=1}^{M} (\sigma_{A_{rs}} + \sigma_{E_{rs}})^2 \begin{bmatrix} tr[Q_A^2] & tr[Q_A Q_E] \\ tr[Q_E Q_A] & tr[Q_E^2] \end{bmatrix}$$

$$= \frac{2tr[(\Sigma_A + \Sigma_E)^2]}{\nu_K} \begin{bmatrix} 1 & -\tau \\ -\tau & \kappa \end{bmatrix}$$

$$K \approx I \Rightarrow \tau \approx 1, \kappa \approx 1$$

$$\approx \frac{2tr[(\Sigma_A + \Sigma_E)^2]}{\nu_K} \begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix}$$

Backup: sampling variance of the point estimator

$$tr[Q_A^2] = tr\left[\frac{(K-\tau I)^2}{\nu_K}\right] = tr\left[\frac{\left(K-\frac{tr[K]}{N}I\right)^2}{\left(tr[K^2]-\frac{tr^2[K]}{N}\right)^2}\right] = tr\left[\frac{K^2-2\frac{tr[K]}{N}KI+\frac{tr^2[K]}{N^2}I}{\left(tr[K^2]-\frac{tr^2[K]}{N}\right)^2}\right]$$

$$= \frac{tr[K^2]-2\frac{tr^2[K]}{N}+\frac{tr^2[K]}{N}}{\left(tr[K^2]-\frac{tr^2[K]}{N}\right)^2} = \frac{1}{\nu_K}$$

$$tr[Q_A Q_E] = tr\left[\frac{(K-\tau I)(\kappa I-\tau K)}{\nu_K^2}\right] = \frac{tr[\kappa KI-\tau K^2-\tau KI^2+\tau^2 IK]}{\nu_K^2}$$

$$= \frac{\frac{tr[K^2]}{N}tr[K]-\frac{tr[K]}{N}tr[K^2]-\frac{tr^2[K]}{N}+\frac{tr^3[K]}{N^2}}{\nu_K^2}$$

$$= \frac{\frac{tr[K]}{N}\left(tr[K^2]-tr[K^2]-tr[K]+\frac{tr^2[K]}{N}\right)}{\left(tr[K^2]-\frac{tr^2[K]}{N}\right)^2} = -\frac{\tau}{\nu_K}$$

Backup: sampling variance of the point estimator

$$tr[Q_E^2] = \frac{tr[(\kappa I - \tau K)^2]}{\nu_K^2} = \frac{tr[\kappa^2 I - 2\kappa\tau K + \tau^2 K^2]}{\nu_K^2}$$

$$= \frac{\kappa\left(\frac{tr(K^2)}{N}N - 2\frac{tr^2[K]}{N} + \frac{tr^2[K]}{N^2}\frac{N}{tr[K^2]}tr[K^2]\right)}{\nu_K^2}$$

$$= \frac{\kappa\left(tr[K^2] - 2\frac{tr^2[K]}{N} + \frac{tr^2[K]}{N}\right)}{\nu_K\left(tr[K^2] - \frac{tr^2[K]}{N}\right)} = \frac{\kappa}{\nu_K}$$

$$var\left[\hat{h}_{SNP}^2\right] = var[f(t)] \approx \frac{\partial f(t)}{\partial t} cov[t] \frac{\partial f(t)}{\partial t^T}$$

$$\approx \frac{2tr[(\Sigma_A + \Sigma_E)^2]}{\nu_K(t_A + t_E)^4}(t_E, -t_A)\begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix}\begin{pmatrix} t_E \\ -t_A \end{pmatrix} = \frac{2tr[(\Sigma_A + \Sigma_E)^2]}{\nu_K(t_A + t_E)^4}(t_A + t_E)^2$$

$$= \frac{2tr[(\Sigma_A + \Sigma_E)^2]}{\nu_K(tr[\Sigma_A] + tr[\Sigma_E])^2} = \frac{2}{\nu_K} \cdot \frac{tr[(\Sigma_A + \Sigma_E)^2]}{(tr[\Sigma_A + \Sigma_E])^2} = \frac{2}{\nu_K} \cdot \frac{tr[\Sigma_P^2]}{(tr[\Sigma_P])^2}$$

Backup: sampling variance of the point estimator

For univariate trait, $tr[\Sigma_P^2] = tr^2[\Sigma_P], \implies var\left[\hat{h}_{SNP}^2\right] = \frac{2}{\nu_K}$

For multi-dimensional trait,

$$\frac{tr[\Sigma_P^2]}{tr^2[\Sigma_P]} = \frac{\sum_{i=1}^{M} \lambda_i^2}{\left(\sum_{i=1}^{M} \lambda_i\right)^2} \leq 1 \implies var\left[\hat{h}_{SNP}^2\right] \leq \frac{2}{\nu_K}$$