Evaluating brain structure traits as endophenotypes using polygenicity and discoverability

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Supplementary Figure

Supplementary Figure 1: Q-Q plots of model fit for cortical surface area

Upper panel (green): M2, Lower panel (blue): M3; "*" indicates best fit model

$\lambda_{\text{obs}}$ indicates the genomic control factor in the observed GWAS summary statistics

$\lambda_{\text{fit}}$ indicates the mean genomic control factor over 100 simulated datasets using estimated parameters from GENESIS
Supplementary Figure 1: Q-Q plots of model fit for cortical surface area
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Supplementary Figure 5: Q-Q plots of model fit for anthropometric measurements
Supplementary Figure 6: Effect size distributions across cortical structures and subcortical volumes

(a) Increased effect size in cortical surface area compared to cortical thickness. In the forest plots, the 50th percentile of ranked sSNP absolute effect size is shown with 95% CIs as error bars. * indicates phenotypes with lower/upper limits of proportion of sSNPs in cluster 1 out of range (>1 or <0, limited to 1 or 0). $ indicates phenotype where the 95% CI lower limit of $\sigma_1^2$ or $\sigma_2^2$ had a negative value and was limited to 0. Thus, the CI for those phenotypes needs caution in interpretation. (b) The point estimates in (a) were mapped to the cortical regions. (c) Effect size distribution comparing across cortical structures and subcortical volumes.
Supplementary Figure 7: The relationship between discoverability, polygenicity and heritability

Pearson’s correlation coefficient (corr) showed (a) significant negative correlation between polygenicity ($\pi_c$) and discoverability (absolute value of effect size). (b) Covariance matrix from GENESIS output indicated a negative correlation between estimates of $\pi_c$ and $\sigma^2$ which is likely producing the negative correlation in (a). We also observed (c) significant positive correlation between heritability ($h^2$) and discoverability, but (d) no significant correlation between heritability and polygenicity. Only phenotypes best fit to M2 were shown in (a) to simplify assessment of the correlation of estimated parameters in the model (b). Error bar indicates 95% CIs of the estimate.

**Category**
- Cortical Surface Area
- Cortical Thickness
- Subcortical Volume
- Neuropsychiatric Disorders
- Addiction Relevant Traits
- Cognition
- Neurodegenerative Disorders
- Anthropometric Measurements
Supplementary Figure 8: Estimates of heritability across multiple complex brain-relevant traits

The estimated SNP-based heritability by GENESIS across traits shows (a) that generally subcortical volume traits have the highest heritability, followed by cortical surface area, and then cortical thickness, and (b) increased heritability of global cortical traits compared to neuropsychiatric disorders, addiction traits, cognition, and anthropometric measurements. (c) The significance after FDR correction between categories, calculated via a heterogeneity test. The horizontal line indicates $-\log_{10}(FDR = 0.05)$.
Supplementary Figure 9: Correlation between measurement error of MRI segmentations and discoverability/polygenicity.

Correlation between measurement error of MRI phenotypes and discoverability/polygenicity. Test-retest correlation (i.e. the similarity between MRI segmentations from two scans of the same individual) for subjects that passed visual inspection was obtained from [Iscan et al., 2015]. The blue line indicates a regression line with 95% confidence intervals. Three regions (temporal pole, frontal pole and entorhinal cortex) with low TRC (<0.7) drove these significant correlations. When these three regions were removed, there was no detectable relationship between genetic architecture and measurement error (r=0.24; p=0.059 for discoverability and r=-0.21, p=0.100 for polygenicity).
Supplementary Figure 10: Correlation between population stratification and discoverability/polygenicity

No association between population stratification and polygenicity. LDSC intercept, a measure of population stratification, vs number of sSNPs, a measure of polygenicity, either including height (left), where population stratification has previously been shown to have a strong effect on summary statistics [Sohail et al., 2019], and without height (right). Pearson’ correlation coefficients suggest no correlation between LDSC intercept and estimated number of sSNPs in either case. While LDSC intercept for height suggests strong population stratification, brain-relevant traits tested in this study do not show strong evidence of population stratification (LDSC intercepts close to 1).
Supplementary Figure 11: Replication in summary statistics from UKBiobank

Comparisons of polygenicity and discoverability from GWAS summary statistics without meta-analysis in the UK Biobank cohort. Similar to findings in Figures 2 & 3, The predicted number of sSNPs shows (a) decreased polygenicity for global cortical traits compared to depression, addiction relevant traits, cognition, and anthropometric measurements. (b) The significance after FDR correction between categories, calculated via a heterogeneity test. The effect size distributions across UKBB traits suggest increased effect sizes in cortical structure compared to depression, addiction relevant traits, cognition and anthropometric measurements (c-e). Joint effect sizes are an approximation of Pearson’s correlation coefficient between sSNPs and phenotype. M2/M3 indicates the best fit model for the traits. (d) A comparison of the absolute effect size at the 50th percentile across traits. The significance between categories under FDR correction, calculated via a heterogeneity test, is displayed in (e). The horizontal line indicates \(-\log_{10}(FDR = 0.05)\) (b,e). All traits shown in this figure are derived from the UKBB summary statistics.
a Cortical Structures

- parac-Desikan_l_area_TotSurf
- parac-Desikan_l_thickness_GlobalMean/Thickness
- parac-Desikan_l_area_TotSurf
- parac-Desikan_r_area_TotSurf

Fixed effect model
Homogeneity: Ψ² = 0%, θ² = 0, p = 0.60

Depression
- broad depression
- softMDD
- probMDD

Fixed effect model
Homogeneity: Ψ² = 0%, θ² = 0, p = 0.57

Cognition
- Intelligence
- Reaction Time

Fixed effect model
Homogeneity: Ψ² = 0%, θ² = 0, p = 0.62

Addiction relevant traits
- Cigarettes per day
- Drinks per week

Fixed effect model
Homogeneity: Ψ² = 0%, θ² = 0, p = 0.58

Anthropometric measurements
- BMI
- Height

Fixed effect model
Homogeneity: Ψ² = 0%, θ² = 0, p = 0.83

b Cortical Structure vs

Cortical Structures
- parac-Desikan_l_area_TotSurf
- parac-Desikan_l_thickness_GlobalMean/Thickness
- parac-Desikan_l_area_TotSurf
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Cognition
- Intelligence
- Reaction Time

Fixed effect model
Homogeneity: Ψ² = 0%, θ² = 0, p = 0.57

Addiction relevant traits
- Cigarettes per day
- Drinks per week

Fixed effect model
Homogeneity: Ψ² = 0%, θ² = 0, p = 0.58

Anthropometric measurements
- BMI
- Height

Fixed effect model
Homogeneity: Ψ² = 0%, θ² = 0, p = 0.83

c Cortical Structure vs

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- softMDD
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Homogeneity: Ψ² = 0%, θ² = 0, p = 0.60

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Anthropometric measurements
- BMI
- Height

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d Cortical Structure vs

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Anthropometric measurements
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Fixed effect model
Homogeneity: Ψ² = 0%, θ² = 0, p = 0.83

Cortical Structure vs
Supplementary Figure 12: Impacts of sample size on discoverability estimates

Three schizophrenia GWASs (Ripke et al. 2013; Ripke et al. 2014; Pardiñas et al. 2018) with different sample sizes ($N_{eff} = 31,519 \sim 99,863$) were compared. Effect sizes were decreased with larger sample numbers (a-c). Effective sample size was calculated by $4/(1/cases+1/controls)$ (Willer et al. 2010).

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**a**

- Ripke et al. 2013 ($N_{eff} = 31,519.4$)
- Ripke et al. 2014 ($N_{eff} = 75,846.1$)
- Pardiñas et al. 2018 ($N_{eff} = 99,863.4$)

**b**

- Higher discoverability
- $-log_{10}$ (probability of observing sSNPs with effect size $>$ x)

**c**

- Fixed effect model
- Heterogeneity: $I^2 = 74\%$, $I^2 < 0.0001$, $p = 0.02$
Supplementary Figure 13: Percentage of GWAS heritability explained by GWS SNPs

Predicted percentages (%) of genetic variance explained by genome-wide significant SNPs (y-axis) are shown with the given sample size (50K to 1.5M). At the right, predicted % of genetic variance explained with sample size of 1.5M are labeled. For regional cortical structures, only regions with the best or worst % of genetic variance explained are labeled.
## Supplementary Table (header information)

### Supplementary Table 1: Study summary

| Header name | Description |
|-------------|-------------|
| Category    | category (e.g. Cortex (Surface Area)) |
| Trait       | trait (e.g. Total Surface Area) |
| Case #      | number of case samples (within case vs control study only) |
| Control #   | number of control samples (within case vs control study only) |
| Total # (effective #) | total sample size (for case vs control study, effective sample number was calculated by $4/(1/case+1/control)$) |
| Ref         | Reference |

### Supplementary Table 2: Estimated sSNPs and heritability from M2 model and model selection

| Header name | Description |
|-------------|-------------|
| Category    | category (e.g. Cortex (Surface Area)) |
| Trait       | trait (e.g. Total Surface Area) |
| GWAS Marker | # of GWAS SNPs after QC |
| # of sSNPs  | number of susceptibility SNPs (and standard error) |
| pi_c        | proportion of sSNPs (and standard error) |
| Heritability| heritability estimates (and standard error) |
| BIC_M2      | modified BIC based on fit of the 2-component model (M2) |
| BIC_M3      | modified BIC based on fit of the 3-component model (M3) |
Ratio | ratio of two variance estimates from M3
---|---
Best-fit Model | final choice of best fit model (see Methods)

Supplementary Table 3: Estimated sSNPs and heritability from M3 model

| Header name | Description |
|-------------|-------------|
| Category    | category (e.g. Cortex (Surface Area)) |
| Trait       | trait (e.g. Total Surface Area) |
| GWASMaker   | # of GWAS SNPs after QC |
| # of sSNPs  | number of susceptibility SNPs (and standard error) |
| pi_c        | proportion of sSNPs (and standard error) |
| Proportion of sSNPs in cluster 1 | proportion of sSNPs (and standard error) in cluster 1 (larger effect sizes) |
| Heritability in cluster 1 | heritability estimates (and standard error) explained by sSNPs in cluster 1 |
| Heritability in cluster 2 | heritability estimates (and standard error) explained by sSNPs in cluster 2 |
| Total Heritability | heritability estimates (and standard error) explained by all sSNPs |
Supplementary Table 4: Predicted sample sizes required to explain the full heritability of traits

| Header name | Description |
|-------------|-------------|
| Category    | category (e.g. Cortex (Surface Area)) |
| Trait       | trait (e.g. Total Surface Area) |
| model       | best fit model (M2 or M3) |
| Required sample # | # of GWAS sample required to pass 99% of heritability explained by GWS sSNPs |
| % of GV     | % of heritability explained by GWS sSNPs at 20 M individuals when it is not expected to pass 99% (in Required sample # column) |