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Model and parameter specification in terms of the observed moments

The GWAS-by-Subtraction model specifies a system of algebraic equations that are fit within Genomic SEM. The complete set of equations is graphically expressed as a path diagram in **Figure 1**. In this diagram, squares represent the observed SNP and the genetic components of the original GWAS phenotypes (Cognitive Performance and Educational Attainment). Circles represent the latent (Cognitive and Noncognitive) genetic components of Cognitive Performance and Educational Attainment. Single-headed arrows represent linear regression associations pointing from the independent variable to the dependent variable, and two-headed arrows represent variances and covariance relationships. Here, we provide the full set of algebraic equations for the GWAS-by-Subtraction model in written (as opposed to graphical) form. We provide the expected (*i.e.*, model-implied) genetic covariance structure (so-called "population moments") as a function of the model parameters, and because the model is perfectly-identified (in the sense of having the same number of free parameters as are present in the genetic covariance matrix being modelled) we provide the algebraic solution for the parameter estimates as a function of the empirically estimated genetic variances and covariances. For clarity, we present the model specification in two sections (LDSC Model and Full Model), but all results for this paper were estimated in a single step (the Full Model).

1. LDSC Model

We begin, for the sake of illustration, with a GWAS-by-subtraction model that does not include a SNP. We refer to this as the LDSC model, as it models LDSC-estimated genetic covariance structure without including SNP effects. The regression equations composing the LDSC model are

$$CP = \lambda_1 Cog$$

$$EA = \lambda_2 Cog + \lambda_3 NonCog$$

and the covariance matrix for the independent variables in the model is

$$cov(Cog, NonCog) = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix},$$

where *CP* and *EA* are the genetic components of the original GWAS phenotypes, Cognitive Performance and Educational Attainment, respectively; *Cog* and *NonCog* are the latent cognitive and noncognitive components of genetic variance scaled to a standardized metric; and λ_1, λ_2 and λ_3 are freely estimated factor loadings that are equivalent to regression weights.

It follows from standard covariance algebra[1] that this model implies the following genetic covariance matrix as a function of the parameters:

$$\widehat{cov}(CP, EA) = \begin{bmatrix} (\lambda_1)^2 & \lambda_1\lambda_2 \\ \lambda_1\lambda_2 & (\lambda_2)^2 + (\lambda_3)^2 \end{bmatrix}$$

In Genomic SEM, numerical optimization is employed to estimate the parameters that minimize the weighted discrepancy between the model-implied genetic covariance matrix and the empirical genetic covariance matrix according to a fit function. The empirical matrix takes the following form

$$cov(CP, EA) = \begin{bmatrix} h^2_{CP} & \sigma_{CP,EA} \\ \sigma_{CP,EA} & h^2_{EA} \end{bmatrix},$$

where h^2_{CP} and h^2_{EA} are the LDSC-estimated SNP heritabilities of cognitive performance and educational attainment respectively, and $\sigma_{CP,EA}$ is the LDSC-estimated genetic covariance between cognitive performance and educational attainment (*i.e.*, the genetic correlation scaled in relation to the respective SNP heritabilities).

In circumstances in which the number of free model parameters are exactly equal to the number of nonredundant elements in the empirical matrix, as is the case here, the model is perfectly identified and a closed-form solution for the model parameters as a function of the elements in the empirical matrix can be straightforwardly obtained. By setting the corresponding elements from the implied and empirical matrices to be equal, we can solve for λ_1 as follows

$$(\lambda_1)^2 = h_{CP}^2,$$

$$\lambda_1 = \sqrt{h_{CP}^2},$$

which we can use to solve for λ_2 as follows

$$\lambda_1\lambda_2 = \sigma_{CP,EA},$$

$$\lambda_2 = \frac{\sigma_{CP,EA}}{\lambda_1} = \frac{\sigma_{CP,EA}}{\sqrt{h_{CP}^2}},$$

which we can in turn use to solve for λ_3 as follows

$$(\lambda_2)^2 + (\lambda_3)^2 = h_{EA}^2$$

$$(\lambda_3)^2 = h_{EA}^2 - (\lambda_2)^2 = h_{EA}^2 - \left(\frac{\sigma_{CP,EA}}{\sqrt{h_{CP}^2}}\right)^2$$

$$\lambda_3 = \sqrt{h_{EA}^2 - \frac{(\sigma_{CP,EA})^2}{h_{CP}^2}}.$$

2. Full Model

We now provide the specification of the GWAS-by-subtraction model that includes a SNP effect. We refer to this as the Full Model, and this was the model fit for our primary analyses in this paper. The regression equations composing the full model are

$$CP = \lambda_1 Cog$$

$$EA = \lambda_2 Cog + \lambda_3 NonCog$$

$$Cog = \beta_1 SNP + u_{Cog}$$

$$NonCog = \beta_2 SNP + u_{NonCog},$$

and the covariance matrix for the independent variables in the model is

$$cov(SNP, u_{Cog}, u_{NonCog}) = \begin{bmatrix} \sigma_{SNP}^2 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix},$$

where β_1 and β_2 are regression effects of of *Cog* and *NonCog* on the SNP; u_{Cog} and u_{NonCog} are residuals of *Cog* and *NonCog* that are not accounted for by the SNP; and σ_{SNP}^2 is the SNP variance. We assume that the LDSC-estimated genetic covariance matrix can be generalized to each SNP individually.

The model-implied genetic covariance matrix as a function of the parameters is

$$\widehat{cov}(SNP, CP, EA) = \begin{bmatrix} \sigma_{SNP}^2 & (\sigma_{SNP}^2)\beta_1\lambda_1 & (\sigma_{SNP}^2)\beta_1\lambda_2 + (2pq)\beta_2\lambda_3 \\ (\sigma_{SNP}^2)\beta_1\lambda_1 & (\lambda_1)^2 + (\sigma_{SNP}^2)(\beta_1\lambda_1)^2 & \lambda_1\lambda_2 + \lambda_1\beta_1(\sigma_{SNP}^2)\beta_2\lambda_3 + \lambda_1(\beta_1)^2(\sigma_{SNP}^2)\lambda_2 \\ (\sigma_{SNP}^2)\beta_1\lambda_2 + (2pq)\beta_2\lambda_3 & \lambda_1\lambda_2 + \lambda_1\beta_1(\sigma_{SNP}^2)\beta_2\lambda_3 + \lambda_1(\beta_1)^2(\sigma_{SNP}^2)\lambda_2 & (\lambda_2)^2 + (\lambda_3)^2 + (\sigma_{SNP}^2)(\beta_1\lambda_2)^2 + (\sigma_{SNP}^2)(\beta_2\lambda_3)^2 \end{bmatrix}.$$

Because SNP effects are individually very small relative to overall SNP heritabilities and genetic covariances, we can simplify the above by setting β_1 and β_2 in the $\widehat{cov}(CP, EA)$ portion of $\widehat{cov}(SNP, CP, EA)$ to zero, producing a simplified model-implied matrix

$$\widehat{cov}(SNP, CP, EA) \approx \begin{bmatrix} 2pq & (2pq)\beta_1\lambda_1 & (2pq)\beta_1\lambda_2 + (2pq)\beta_2\lambda_3 \\ (2pq)\beta_1\lambda_1 & (\lambda_1)^2 & \lambda_1\lambda_2 \\ (2pq)\beta_1\lambda_2 + (2pq)\beta_2\lambda_3 & \lambda_1\lambda_2 & (\lambda_2)^2 + (\lambda_3)^2 \end{bmatrix}.$$

The empirical matrix takes the following form

$$cov(SNP, CP, EA) = \begin{bmatrix} 2pq & (2pq)\beta_{CP} & (2pq)\beta_{EA} \\ (2pq)\beta_{CP} & h^2_{CP} & \sigma_{CP,EA} \\ (2pq)\beta_{EA} & \sigma_{CP,EA} & h^2_{EA} \end{bmatrix},$$

where *p* is the minor allele frequency of the SNP, and *q* is 1-*p*; β_{CP} and β_{EA} are the GWAS regression coefficients for the SNP from the original CP and EA summary statistics, respectively. In practice, minor allele frequency is obtained from a reference panel, but because *2pq* cancels out from the below derivations, the source of minor allele frequency information is of limited consequence.

Note that the elements in the simplified $\widehat{cov}(CP, EA)$ portion of $\widehat{cov}(SNP, CP, EA)$ are solved for as a function of the elements in the empirical matrix as in the LDSC model. To solve for the remaining terms in the Full model (σ^2_{SNP}, β_1 and β_2), as a function of the elements in the empirical matrix, we equate the corresponding elements of the implied and empirical matrices, simplify, and substitute.

For σ^2_{SNP}, we have

$$\sigma^2_{SNP} = 2pq,$$

for β_1, we have

$$(2pq)\beta_1\lambda_1 = (2pq)\beta_{CP}$$

$$\beta_1 = \frac{\beta_{CP}}{\lambda_1} = \frac{\beta_{CP}}{\sqrt{h^2_{CP}}},$$

and for β_2 we have

$$(2pq)\beta_1\lambda_2 + (2pq)\beta_2\lambda_3 = (2pq)\beta_{EA}$$

$$\beta_2\lambda_3 = \beta_{EA} - \beta_1\lambda_2$$

$$\beta_2 = \frac{\beta_{EA} - \beta_1\lambda_2}{\lambda_3} = \frac{\beta_{EA} - \frac{\beta_{CP}}{\sqrt{h^2_{CP}}}\frac{\sigma_{CP,EA}}{\sqrt{h^2_{CP}}}}{\sqrt{h^2_{EA} - \frac{(\sigma_{CP,EA})^2}{h^2_{CP}}}} = \frac{\beta_{EA} - \frac{\beta_{CP}\,\sigma_{CP,EA}}{h^2_{CP}}}{\sqrt{h^2_{EA} - \frac{(\sigma_{CP,EA})^2}{h^2_{CP}}}}.$$

When running GWAS-by-subtraction, we assume, as with any model, that the model defined is correctly specified. Therefore, *Cog* is assumed to cause EA and CP and all genetic influences on CP operate via effects on *Cog*. Thus, the model assumes that all genetic effects on CP also affect EA. This assumption is reasonable here, as cognitive ability can reasonably be assumed to be an important causal driver of educational success. For any pair of traits subjected to GWAS-by-subtraction a similar consideration of the validity of the model needs to be made[2].

A practical tutorial to run a GWAS-by-subtraction using GenomicSEM is available at:
https://rpubs.com/MichelNivard/565885

SNP filtering steps

Running a GWAS-by-subtraction assumes the genetic covariance between traits, as estimated using LD score regression implemented in GenomicSEM, is consistent across SNPs. That is, we assume that the LDSC-estimated genetic covariance matrix can be generalized to each SNP individually. (The same assumption holds for other

GenomicSEM[3] models and alternate software like MTAG,[4] where this assumption is referred to as the homogenous-Omega assumption).

To help ensure this assumption is met, the SNPs included in all input GWASs are filtered to a set of SNPs that are present in a substantial number of studies.

The first SNP filtering steps take place when running the (meta-analysed) GWASs of EA and CP:

- **EA GWAS**: We meta-analysed public summary statistics of Lee et al.[5] (*N*=766,345) with 23andMe (N = 365.538): We included SNPs with sample-size > 500,000 and MAF > 0.005 in the 1000 Genomes reference set (10,101,243 SNPs). As 23andMe sample size was 365.538, SNPs only present in 23andMe were not included. The UKB sample in the Lee summary statistics is 442,183, so SNPs only present in UKB are also not included.
- **CP GWAS**: The public summary statistics by Lee et al. result from a meta-analysis of COGENT data (35 cohorts, N = 35,298) and UKB (N = 222,543). Lee et al. "impos[ed] a minimum-sample-size filter of 100,000, leaving 10.10M SNPs". It is therefore possible that SNPs only present in UKB are present in the CP GWAS.

When running the GWAS-by-subtraction in Genomic SEM, additional SNP filtering is performed. SNPs with MAF<0.01 (according to the reference SNPs from HapMap3) are excluded. Additionally, filtering on SNPs present in the 1000 Genomes Phase is done. As *Cog* and *NonCog* GWAS results are obtained from the GWAS-by-subtraction analysis of EA and CP GWASs, only SNPs present in both EA and CP GWAS are present in the Cog and NonCog GWAS (7,311,269 SNPs).

Effective sample size calculation

We adapted the method for effect sample size calculation from Mallard, T. T., et al (2020).[6] First, we assume that the effect of SNP j follows

$$est_j = \frac{Z_j}{\sqrt{n_j \times 2 \times MAF_j\left(1 - MAF_j\right)}}$$

where Z is the z-score of that SNP, n is the sample size of that SNP, and MAF is the minor allele frequency of that SNP (note: the variance of SNP j (σ_j^2) is estimated as $2 \times MAF_j\left(1 - MAF_j\right)$). Therefore, if we know the effect and MAF of that SNP, then we can estimate its effective sample size by solving for n_j:

$$\frac{est_j}{Z_j} = \frac{1}{\sqrt{n_j \times \sigma_j^2}}$$

$$\frac{Z_j}{est_j} = \sqrt{n_j \times \sigma_j^2}$$

$$\left(\frac{Z_j}{est_j}\right)^2 = n_j \times \sigma_j^2$$

$$n_j = \frac{(Z_j/est_j)^2}{\sigma_j^2}$$

This formula will typically produce reasonable estimates of n_j, but it can be prone to error for SNPs with low MAF. As such, we set a lower and upper MAF limit of 10% and 40%, respectively, when estimating effective N for the overall

multivariate GWAS results (N_{eff}). Following this, we estimate that N_{eff} is approximately equal to the mean n_j for m SNPs with a MAF between a and b. This can be expressed as follows:

$$N_{eff} \approx \frac{1}{m} \sum_{MAF=a}^{b} n_j$$

As we applied this formula to summary statistics for the Cholesky model, we adjusted the estimates est_j by multiplying them by the residual heritability (In **Figure 1**: λNonCog-EA for NonCog and λCog-CP for Cog), such that

$$n_j = \frac{(Z_j/(est_j \times \lambda))^2}{\sigma_j^2}$$

Probing potential biases resulting from cohort differences in SNPs

Genomic SEM uses LD score regression to estimate the cross-trait LD score intercept, a parameter that quantifies the portion of covariance between GWAS summary statistics attributable to sample overlap and phenotypic covariance in the overlapping samples. The cross-trait LD score intercept is used when estimating the SNP effects to account for sample overlap. If, however, SNPs are not present in all discovery cohorts, this parameter might be biased. This potential for bias is mitigated by imposing a minimum N for included SNPs (see **Supplementary Note** on SNP filtering), but we took additional steps to consider this issue.

In our current application the largest potential biases arise from SNPs in the CP GWAS that are present in UKB, but not COGENT. The minimum sample size used to filter SNPs means that SNPs that were missing in UKB or 23andme cohorts in the EA GWAS (the largest cohorts) would be omitted from our analyses. Far smaller biases may occur for SNPs that were not present in the GWAS summary data provided by smaller contributing cohorts.

In our specific analysis, 128,376 out of 7,311,269 SNPs (1.8%) are not present in COGENT. All but one of the genome-wide hits for *Cog* and *NonCog* are present in COGENT. The missing hit is a *Cog* hit, and a proxy for the lead SNP is present in COGENT and is genome-wide significant ($p < 5x10^{-8}$). Of these SNPs a mere 2847 (< 0.3%) are in the HapMap3 set typically used for LD score regression, and in our case, used in computing genetic correlations and LDSC-based bio-annotation. Thus, these analyses are unlikely to be affected by bias resulting from SNPs being present missing in COGENT.

However, in future applications of GWAS-by-subtraction, selective availability of loci could be a considerable source of bias. We, therefore, offer an outline of a workflow that could be used to mitigate this issue in future applications.

Workflow

- For each individual set of GWAS summary statistics, stringently filter to retain only SNPs analysed in the majority of contributing studies.
- Use DIST[7], or other suitable tool, and a suitable reference LD panel, to impute the missing SNPs in all GWAS summary statistics files used in a GenomicSEM analysis. Example code and software: http://dleelab.github.io/dist/
- Estimate the genetic covariance using ldsc() *omitting the SNPS imputed with DIST at R2 or INFO < .9* . These SNPs are omitted in this step, because poorly imputed SNPs are known to downwardly bias the LD score regression slope.
- Run a GWAS in GenomicSEM considering all SNPs, imputed or otherwise

The workflow does not rely on SNPs present in a minority of cohorts, reducing bias. It does, however, inherit all assumptions from DIST or other tool used to impute a complete set of SNP effect sizes from summary data and an LD reference.

Probing potential biases due to cohort differences in SNP heritability

In addition to probing potential biases due to incomplete overlap in SNPs present in contributing cohorts, we also explored possible consequences of cohort differences in SNP heritability. Notably the GWAS of CP results from a meta-analysis of a GWAS in UKBiobank and a GWAS in multiple cohorts from the COGENT consortium[5,8]. The SNP heritability of CP in COGENT and UKBiobank is different (COGENT $h^2 = 0.1318$ (0.0156), UKB $h^2 = 0.2163$ (0.0077)). As a sensitivity analysis to explore the possible consequences of this fact, we ran a model (**Supplementary Figure 2**) in which COGENT and UKB CP were included as separate variables loading on *Cog*, but not *NonCog*. EA still loads on *Cog* and *NonCog*.

We re-analyzed all 437 independent genome-wide significant loci (for *Cog* and *NonCog*) from the model used in the remainder of the paper (**Figure 1**) and this alternative model, which allows the heritability to differ between COGENT and UKB (**Supplementary Figure 2**). We observed negligible differences in effect sizes, or Z-statistic between the two models ($r > 0.99$) (**Supplementary Figure 3**). We proceed to re-compute the genetic correlations with all external complex traits in **Figure 4** and **Supplementary Figure 11** (by adapting the model **Supplementary Figure 17**). Again, we observe no meaningful differences ($r > .99$ for *Cog* and for *NonCog* rGs, **Supplementary Figure 4** and **Table 5**). Therefore, cohort differences in SNP heritability in the CP GWAS seems to have a minimal impact on our results.

Sensitivity test for non-zero correlation of *Cog* and *NonCog*

When running GWAS-by-subtraction we assume the model as defined is a correct representation of the relation between cognitive performance (CP) and educational attainment (EA). As the *Cog* and *NonCog* latent factors are specified to be uncorrelated, all SNPs that influence *Cog* will effect both CP and EA, and all SNPs influencing *NonCog* will only influence EA.

To investigate how a positive non-zero correlation between the *Cog* and *NonCog* latent factors could affect results, we re-ran the Genomic-SEM model setting the standardized covariance (*i.e.*, correlation) of *NonCog* and *Cog* to 0, 0.1, 0.2, and 0.3. At higher levels of correlation between *NonCog* and *Cog*, the *NonCog* factor explained an increasing percentage of variance in EA: 57% with rG(*Cog*, *NonCog*)=0 increasing to 78% when rG(*Cog*, *NonCog*)=0.3. We report the path loadings and the percentage of EA genetic variance explained in **Supplementary Table 6**.

We next re-estimated genetic correlations of *NonCog* and *Cog* with the set of traits in **Figure 4** and **Supplementary Figure 11**. We performed this analysis using models that again set the correlation *NonCog* and *Cog* to 0, 0.1, 0.2, and 0,3, as shown in **Supplementary Figure 17** for rG(*Cog, NonCog*)=0. Results show a consistent pattern of change in *NonCog* rG with target traits. As the correlation of *NonCog* and *Cog* is increased, the *NonCog* rG with a target trait changes in the direction of the rG of *Cog* with that trait. For example, in the case of household income, *Cog* is positively associated with the trait, therefore as the rG(*Cog, NonCog*) increases, the correlation of household income with NonCog increases positively (at rG(*Cog, NonCog*)=0 the rG is 0.61, at rG(*Cog, NonCog*)=0.3 it is 0.76). These changes are small in magnitude, but sometimes alter the statistical significance of the rG. When rG(*Cog, NonCog*) is set to 0.3, the following rGs with *NonCog*, which were not statistically different from zero under the rG(*Cog, NonCog*)=0 specification, become statistically significant: Age at menopause, Autism Spectrum Disorder and Chronotype. In contrast, only Conscientiousness and Self-report empathy had a statistically significant rG with *NonCog* under rG(*Cog, NonCog*)=0 but were not significantly genetically correlated with NonCog when when rG(*Cog, NonCog*)=0.3. Results are presented in **Supplementary Table 7** and **Supplementary Figure 5**.

The magnitude of the change of the genetic correlation with *NonCog* is dependent on the genetic correlation of *Cog* with the trait: the stronger the genetic correlation with *Cog*, the bigger increase/decrease of the genetic correlation with *NonCog* (**Supplementary Figure 6**).

Sensitivity test for causal relation between CP and EA

Our primary model (**Figure 1**) assumes all genetic effects on CP also affect EA. This assumption is reasonable here**,** as cognitive ability is an important driver of educational success. In fact, many high-income countries mandate cognitive test-scores as entry to higher education. Furthermore, tests of polygenicity consistently find that a smaller portion of the genome has an effect on CP then on EA, consistent with a model where CP causes EA.

However, we can consider a violation of our assumed model based on reasonable estimates from the literature. Ritchie and Tucker-Drob (2018)[9] find across multiple studies, which rely on control variables or natural experiments, that there is a robust but small effect of education on IQ. Consistent with these results, Savage et al. (2018)[10] performed a GWAS of intelligence and, using Mendelian randomization, found a bidirectional effect between IQ and educational attainment.

We investigated the impact of a reciprocal effect of EA on CP on our results. We can only allow for, but not estimate, such an effect in the context of our model, as the effect is not identified (**Supplementary Figure 7**); we chose a small standardized effect size of 0.2. Based on this alternative model, we reanalyzed the genome-wide significant SNPs for *Cog* and *NonCog* and found minimal change in Z-statistics (see **Supplementary Figure 8**). We further re-computed the genetic correlations between *Cog* and *NonCog* and the external traits in **Figure 4** and **Supplementary Figure 11** (by adapting the model **Supplementary Figure 17**). We observe minimal changes in the genetic correlations as well (**Supplementary Figure 9** and **Table 8**). Therefore, our results appear robust to the relaxation of the assumption that the primary causal relationship is from CP to EA and not vice versa.

Cohort descriptions

National Longitudinal Study of Adolescent to Adult Health (Add Health). Add Health[11] is a longitudinal study of a nationally representative sample of adolescents in grades 7-12 in the United States during the 1994-95 school year. Beginning with an in-school questionnaire administered to a nationally representative sample of students in grades 7-12, the study followed up with a series of in-home interviews conducted in 1995, 1996, 2001-02, 2007-08, and 2016-2018. A sample of 80 high schools and 52 middle schools from the US was selected with unequal probability of selection. Incorporating systematic sampling methods and implicit stratification into the Add Health study design ensured this sample is representative of US schools with respect to region of country, urbanicity, school size, school type, and ethnicity. Detailed information on each data collection wave is available at the following link: https://www.cpc.unc.edu/projects/addhealth/faqs/index.html

Add Health participants provided written informed consent for participation in all aspects of Add Health in accordance with the University of North Carolina School of Public Health Institutional Review Board guidelines that are based on the Code of Federal Regulations on the Protection of Human Subjects 45CFR46: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html. The National Longitudinal Study of Adolescent to Adult Health received IRB approval from the University of North Carolina.

Dunedin Longitudinal Study. The Dunedin Study[12] is a longitudinal investigation of health and behavior in a population-representative birth cohort. Participants (N = 1,037; 91% of eligible births; 52% male) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand (NZ), who were eligible based on residence in the province and participation in the first assessment at age 32. The cohort represented the full range of socioeconomic status in the general population of NZ's South Island and, as adults, matches the NZ National Health and Nutrition Survey on key adult health indicators (e.g., body mass index, smoking, general practitioner visits) and same-age

citizens in the NZ Census on educational attainment. The cohort is primarily white (93%). Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38, and most recently (completed April 2019) 45years, when 94% (N = 938) of the 997 living Study members participated. Study protocols were approved by the institutional ethical review boards of the participating universities, and written informed consent was obtained from all Study members. At each assessment, Study members were brought to the research unit for interviews and examinations. The Dunedin Study received ethical approval: 17/STH/25/AM05 Health and Disability Ethics Committees Ministry of Health 133 Molesworth Street PO Box 5013 Wellington 0800 4 ETHICS hdecs@moh.govt.nz

E-Risk Longitudinal Twin Study. The Environmental Risk (E-Risk) Longitudinal Twin Study tracks the development of a birth cohort of 2,232 British children. The sample was drawn from a larger birth register of twins born in England and Wales in 1994-1995.[13] Full details about the sample are reported elsewhere.[14] Briefly, the E-Risk sample was constructed in 1999-2000, when 1,116 families (93% of those eligible) with same-sex 5-year-old twins participated in home-visit assessments. This sample comprised 56% monozygotic (MZ) and 44% dizygotic (DZ) twin pairs; sex was evenly distributed within zygosity (49% male). 90% of participants were of white ethnicity. Families were recruited to represent the UK population with new-borns in the 1990s, to ensure adequate numbers of children in disadvantaged homes and to avoid an excess of twins born to well-educated women using assisted reproduction. The study sample represents the full range of socioeconomic conditions in Great Britain, as reflected in the families' distribution on a neighbourhood-level socioeconomic index (ACORN [A Classification of Residential Neighbourhoods], developed by CACI Inc. for commercial use).[15,16] Specifically, E-Risk families' ACORN distribution matches that of households nation-wide: 25.6% of E-Risk families live in "wealthy achiever" neighbourhoods compared to 25.3% nationwide; 5.3% vs. 11.6% live in "urban prosperity" neighbourhoods; 29.6% vs. 26.9% live in "comfortably off" neighbourhoods; 13.4% vs. 13.9% live in "moderate means" neighbourhoods, and 26.1% vs. 20.7% live in "hard-pressed" neighbourhoods. E-Risk underrepresents "urban prosperity" neighbourhoods because such houses are likely to be childless. Follow-up home visits were conducted when the children were aged 7 (98% participation), 10 (96%), 12 (96%), and at 18 years (93%). There were 2,066 children who participated in the E-Risk assessments at age 18, and the proportions of MZ (56%) and male same-sex (47%) twins were almost identical to those found in the original sample at age 5. The average age of the twins at the time of the assessment was 18.4 years (SD = 0.36); all interviews were conducted after their 18th birthday. There were no differences between those who did and did not take part at age 18 in terms of socioeconomic status (SES) assessed when the cohort was initially defined ($\chi 2$= 0.86, p= .65), age-5 IQ scores (t= 0.98, p= .33), or age-5 emotional or behavioural problems (t= 0.40, p= .69 and t= 0.41, p= .68, respectively). 49% of participants at age 18 were educated to A-Level (the school leaving qualification in the United Kingdom) while 29% had GCSEs at grade A*-C as their highest qualification (obtained at approximately 14-16 years). 71% of participants were currently studying and 57% were in work. 12% were neither in education or work at the time of the assessment. Home visits at ages 5, 7, 10, and 12 years included assessments with participants as well as their mother (or primary caretaker). The home visit at age 18 included interviews only with the participants. The Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee approved each phase of the study. Parents gave informed consent and twins gave assent between 5-12 years and then informed consent at age 18.

The E-Risk study received ethical approval from Duke University Campus IRB Protocol: 2018-0414B0630 The Environmental Risk Study of Twin Development and Replication Data Studies

Texas Twins Project. The Texas Twin Project[17] is a diverse population-based registry of twins in Austin, Texas and the surrounding areas. From 2013, the Texas Twin Project has recruited more than 3,000 child and adolescent twins (~1,500 pairs) who have participated in in lab-based studies. Participants closely resemble the racial, ethnic, and socioeconomic diversity of the Austin area, as approximately one-third of participants (31%) have received food stamps or another form of means-tested public assistance. Females comprise approximately 50% of the sample. Participants have been recruited from the Austin metropolitan area notable for racial/ethnic and economic diversity. The Texas Twins sample to be 59% non-Hispanic White, 25% Hispanic/Latino, 9% Black/African American, and 7% another race/ethnicity, including Asian-American and Native American, or multiracial. For our analysis, we only included non-Hispanic White participants, due to the low portability of PGS between different ancestry populations. Approximately one third of the Texas Twins families (31%) have reported having received food stamps or another form of means-tested public assistance. All participants were enrolled in elementary school, middle or high school

within the Texas public school system at the time of data collection. Thus 100% of participants was under age 18 at the time of data collection. Parents of all participants gave informed consent, and children gave informed assent, prior to participation in the study. Inclusion of children was necessary because the focus of the Texas Twin Project is investigating variation in cognitive development and school achievement. The Texas Twin Project has received IRB approval from the University of Texas at Austin (Protocol Number 2014-11-0021), which was renewed on 11/20/2017.

Netherlands Twin Register. The Netherlands Twin Register (NTR) was established around 1987 by the Department of Biological Psychology at the Vrije Universiteit Amsterdam. It recruits approximately 40% of new-born twins or higher-order multiples in the Netherlands for longitudinal research. Parents of twins fill in a survey about the development of their children every 2-3 years until they are 12 years old. From age 14, the adolescents are invited to self-report. Adult twins are registered with the NTR through several approaches (i.e. recruitment through city council offices in the Netherlands, advertising in NTR newsletters and the internet). Parents, siblings, spouses and offspring of adult twins are also invited to take part. Since 1991, participants receive a survey every 2 to 3 years with questions on, amongst others, health, personality, and lifestyle. The NTR has also been collecting genotype data in both children and adults in several large projects, adding to 23 601 genotyped participants (58 % female). More details concerning the NTR's data collection, the methods of recruitment, participants' background and response rates are described elsewhere[18]. Ethical approval was provided by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam, an Institutional Review Board certified by the U.S. Office of Human Research Protections (IRB number IRB-2991 under Federal-wide Assurance-3703; IRB/institute codes 94/105, 96/205, 99/068, 2003/182, 2010/359) and participants provided informed consent.

Wisconsin Longitudinal Survey. The Wisconsin Longitudinal Study (WLS) is a survey based on a 1/3 sample of all 1957 Wisconsin high school graduates and their randomly-selected siblings. The graduate respondents answered in-person questionnaires at age 18 (in 1957), 25, 36, 54, 65, and finally 72 in 2011. Over time 18,129 graduates and siblings contributed data. The WLS sample is broadly representative of white, non-Hispanic American men and women who have completed at least a high school education. About 19 percent of the WLS sample is of farm origin, which is consistent with national estimates in cohorts born in the late 1930s. The WLS includes a wide range of administrative and prospectively collected data from early life through adulthood. More details is reported elsewhere[19] and on the WLS website (https://www.ssc.wisc.edu/wlsresearch/about/description.php). Our usage of the Wisconsin Longitudinal Study data was ethically approved by the Human Subjects Committee of the Faculty of Economics, Business Administration and Information Technology at the University of Zurich (OEC IRB # 2018-049).

Genetic correlation with hold-out-sample EA

To compute rG among *NonCog*, *Cog,* and educational attainment, we re-ran the Genomic-SEM model using summary statistics that omitted the 23andMe sample from the EA GWAS. We then computed the rG between *NonCog* (estimated without 23andMe) and EA in the 23andMe sample. This analysis differed from the original Genomic-SEM analysis of *NonCog*. In that original analysis, $rG(EA,Cog)^2 + rG(EA,NonCog)^2 = 1$. In order to estimate the genetic correlation between *NonCog* and EA free from this constraint, we repeated our Genomic-SEM analysis holding out the 23andMe sample. We then computed the genetic correlation between the new *NonCog* factor and 23andMe summary statistics for EA. This analysis allowed us to compute genetic correlation of *NonCog* with EA based on entirely independent GWAS samples.

PGS analysis of personality traits

We conducted PGS analysis of Big-5 personality in the NTR, Texas Twin, AddHealth, and WLS cohorts (N = 21,203 - 21,290 across personality traits) (**Supplementary Figure 12)**. *NonCog* PGS associations with personality traits paralleled genetic correlations but were smaller in magnitude and were statistically different from zero at the alpha=0.05

threshold only for Openness (meta-analytic β=.13 (*SE*=.02)) and Agreeableness (meta-analytic β=.04 (*SE*=.02)). Also parallel to genetic correlation analysis, the *Cog* PGS associations with openness and neuroticism were in the same direction but smaller in magnitude as compared to *NonCog* associations, and were in the opposite direction for conscientiousness, extraversion, and agreeableness, although only associations with openness, conscientiousness, and neuroticism were statistically different from zero at the alpha=0.05 level (meta-analytic $\beta_{Neuroticism}$=-.05, p_{diff}=<.0001; $\beta_{Openness}$=.08, p_{diff}=.152; $\beta_{Conscientiousness}$=-.03, p_{diff}=.001). Dunedin and E-Risk data on personality traits were not used in these meta-analyses as the measures in these cohorts are informant reports, the other cohorts' measures being self-report.

Cell-type enrichment with Stratified LDSC regression

Additionally to MAGMA[20] analysis, we tested for cell-type specific gene-sets enrichments with stratified LDSC regression[21]. Enrichment in MAGMA tests the enrichment of a particular gene-set relative to all genes. In contrast, enrichment in LD score regression implies enrichment over and above the signal present in any of the "baseline" annotations, which include genes, promoters, histone marks, and other salient features of the genome. Using LDSC partitioned heritability, we found similar results as with MAGMA. The Spearman rank correlation between –log(*p*) of MAGMA estimate and LDSC Enrichment[22] was 0.89 for *NonCog* and 0.83 for *Cog*, indicating a similar cell-type ranking obtained with both methods. However, fewer cell-types are significantly enriched using stratified LDSC (**Supplementary Figure 15** and **Table 19**). For the *NonCog* factor, only one depletion was found for vascular cell (VECC). For the *Cog* factor, only telencephalon projecting neurons, telencephalon interneurons, vascular cells and a di- and mesencephalon neuron (MEGLU7) were found enriched with LDSC, while cell-types in all categories except immune cells, sympathetic neurons and vascular cells were found enriched with MAGMA. One notable difference for *Cog* is the significant depletions in vascular cells found in LDSC, while this is not significant using MAGMA. Nevertheless, as with MAGMA, the correlation between the LD score regression *Z*-statistics for *Cog* and *NonCog* was substantial (*r*=.62). Both by using Equation 1 or jackknifed estimates, there was no significant difference in cell-type specific enrichment between the two factors.

Transcriptome-wide association study

It is somewhat surprising that while *Cog* and *NonCog* are genetically uncorrelated by design, the heritable signal for either is enriched in the same cell-types. This points to enrichment in the same cells being driven by distinct sets of genes. In order to investigate, we used the Fusion tool[23] to conduct transcriptome-wide analysis (TWAS) of *NonCog* and *Cog.* The analysis integrates the SNP effect on gene expression (eQTL effects) and GWAS results to arrive at an estimate of the effect of gene expression on *Cog* and *NonCog.* This analysis revealed that, as expected, the effects of genes on the latent traits Cog and NonCog differ (**Supplementary Table 20**). The correlation between the Z-statistics for the association with *NonCog* and *Cog* was negative (-0.3), although less-negative than expected given that the LD score cross-trait intercept between *Cog* and *NonCog* was estimated at -0.67. The reason for the negative LD score cross-trait intercept is the dependence of the results between our two GWAS induced by sample overlap and the joint estimation of *Cog* and *NonCog* SNP effects within the same model. We plot the distribution of the expected dependence under the null and superimpose the true TWAS results for *Cog* and *NonCog* in **Supplementary Figure 16**. This result is consistent with the overall negative correlation between *NonCog* and *Cog* TWAS results being a function of the sample overlap, with true signal departing from the null-distribution both in concordant and discordant directions.

Genetic correlations with white matter microstructure

We tested genetic correlation of *NonCog* and *Cog* with white matter tract integrity as measured using diffusion tensor imaging (DTI)[24]. Analyses included 5 DTI parameters in each of 22 white matter tracts (**Supplementary Table 22**):

fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and mode of anisotropy (MO).

We first analysed tract-wide association of *NonCog* and *Cog* with the five DTI parameters. *Cog* was nominally associated with global white matter microstructure for two DTI parameters – average AD (r_g=.09 (*SE*=.04); greater diffusion of water along the principal axis of diffusion) and average MO (r_g=.11 (*SE*=.04); more tubular, as opposed to planar, water diffusion). Only average MO survived FDR correction (q=.014). These genetic correlations did not differ from genetic correlations with the *NonCog* factor (χ^2 p >.324).

Next, we analysed tract-specific genetic correlations for each of the 5 DTI parameters. *NonCog* was positively associated with MO in the corticospinal tract (r_g=.14 (*SE*=.05)), retrolenticular limb of the internal capsule (r_g=.12 (*SE*=.04)) and splenium of the corpus callosum (r_g=.10 (*SE*=.04); **Figure 5**), whereas the *Cog* factor was not associated with any specific tracts. However, none of the FDR-significant associations for *NonCog* were statistically different from associations for *Cog* (p_{diff_fdr}=.89-.99), possibly reflecting a lack of power to detect differences in small effects (GWAS based on DTI data of 17,706 participants).

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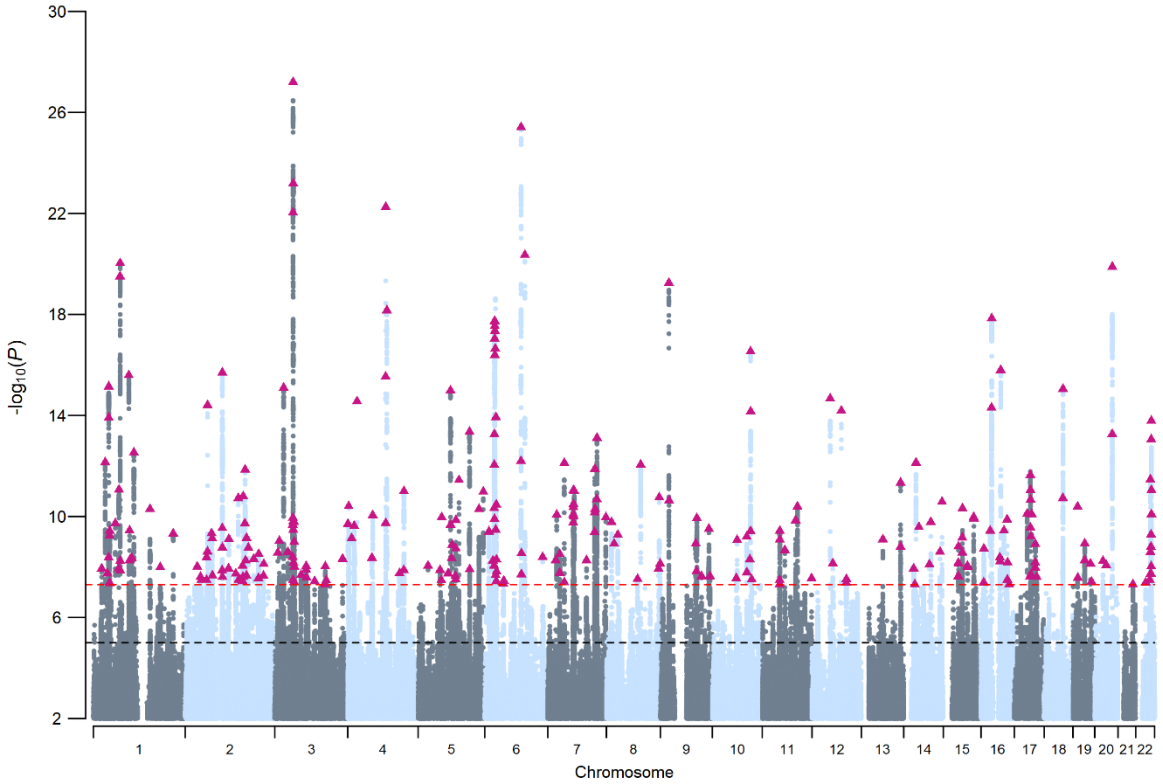
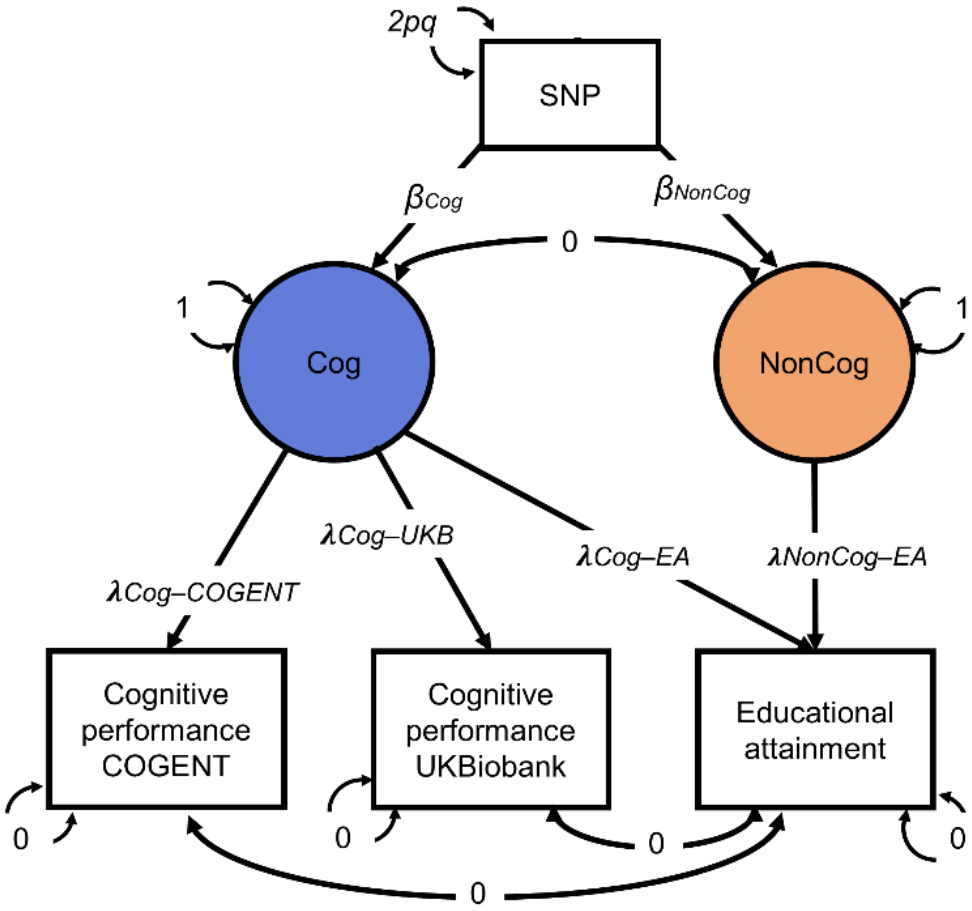
Supplementary Figures

Supplementary Figure 1. Manhattan plot of the *Cog* GWAS

Plot of the -$\log_{10}$(p-value) associated with the Wald test (two-sided) of β_{Cog} for all SNPs ordered by chromosome and base position. Purple triangles indicate genome-wide significant ($p < 5e10^{-8}$) and independent (within a 250Kb window and $r^2 < .1$) associations. The red dashed line marks the threshold for genome-wide significance ($P = 5 \times 10^{-8}$), and the black dashed line the threshold for nominal significance ($P = 1 \times 10^{-5}$).

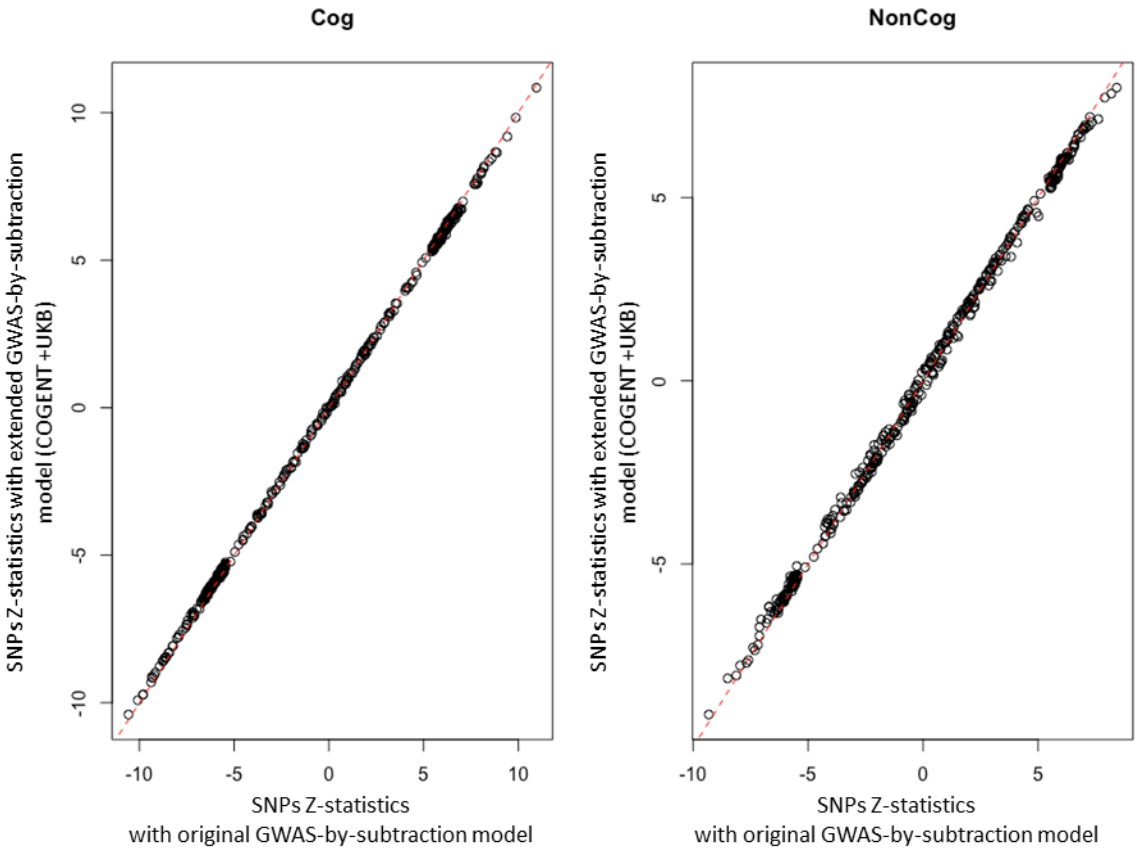


Supplementary Figure 2. Extension of the GWAS-by-subtraction model for Genomic SEM to include two Cognitive Performance GWASs: one in UKBiobank and one from the COGENT consortium

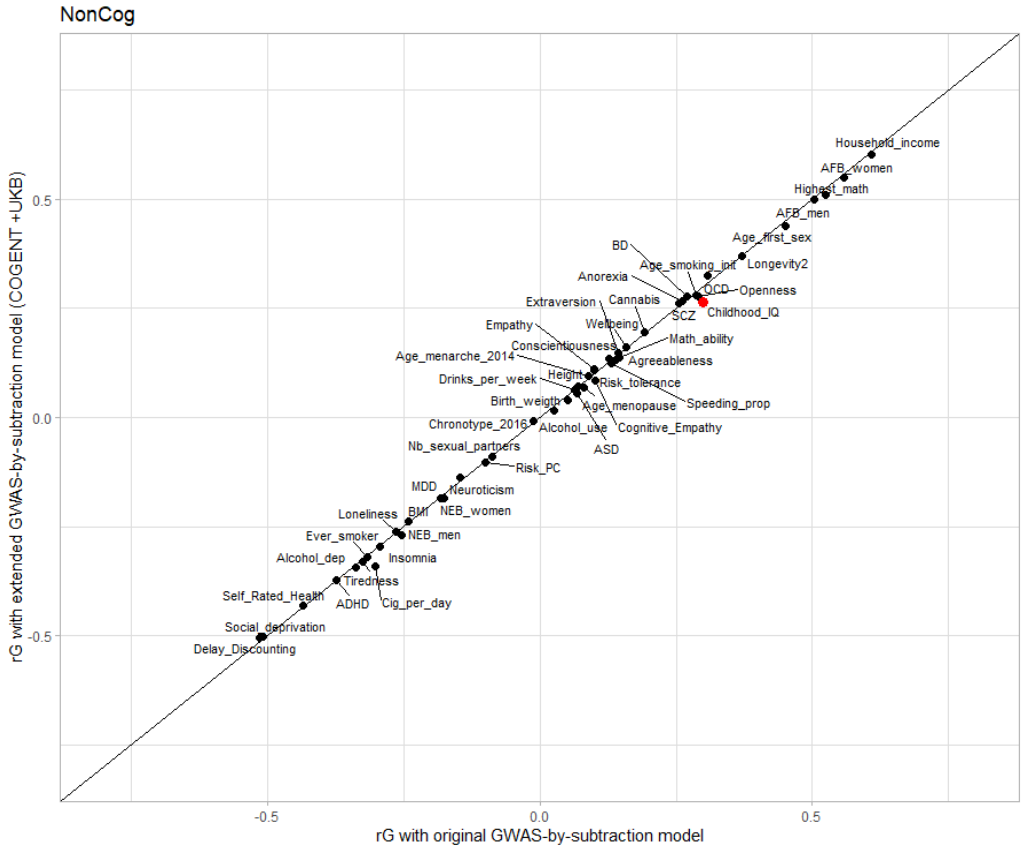


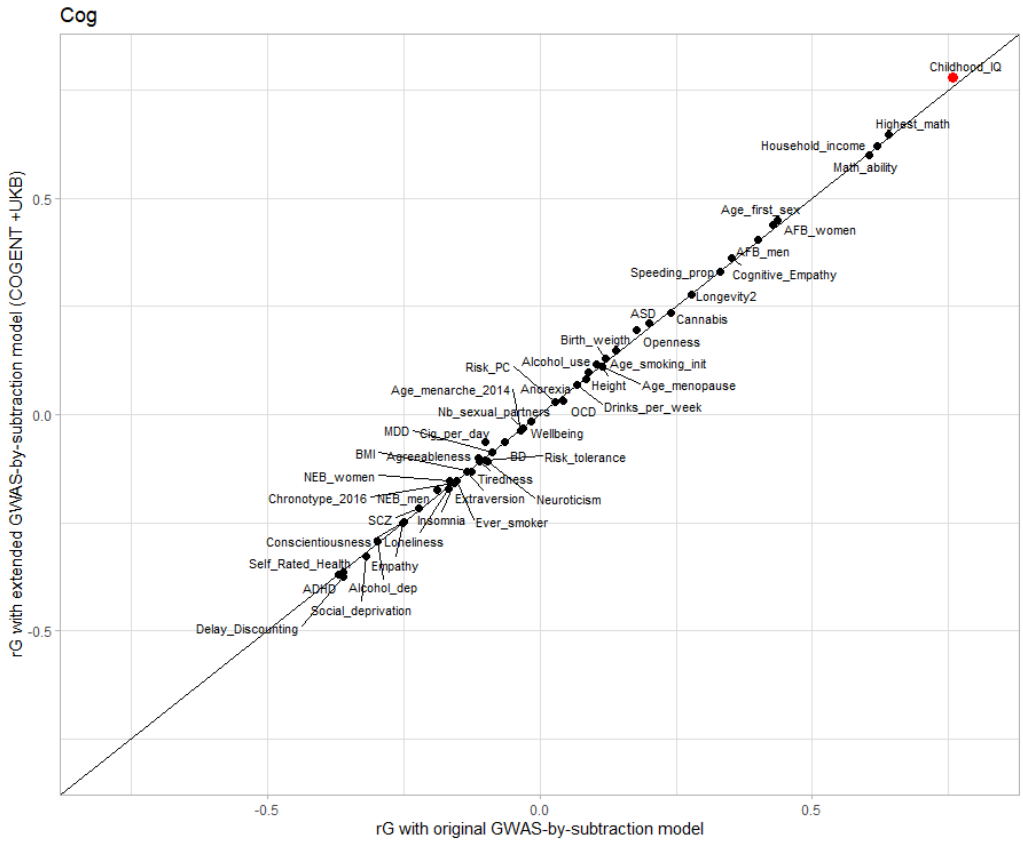
Supplementary Figure 3. Plot of the Z-statistics of the hits SNPs as estimated with our original GWAS-by-subtraction model (Figure 1) vs as estimated with our extended GWAS-by-subtraction to include COGENT and UKB CP GWAS separately (Supplementary Figure 2) for Cog and for NonCog.

The SNPs whose the Z-statistics were estimated correspond to the independent genome-wide significant SNPs for Cog or NonCog as found with model in Figure 1.



Supplementary Figure 4. Plot of the estimates of the genetic correlation of Cog and NonCog with selected phenotypes as estimated with the original GWAS-by-Subtraction model (Figure 1) versus as estimated with our extended GWAS-by-Subtraction to include COGENT and UKB CP GWAS separately (Supplementary Figure 2) for Cog and for NonCog.
Correlation with Childhood IQ is highlighted in red.



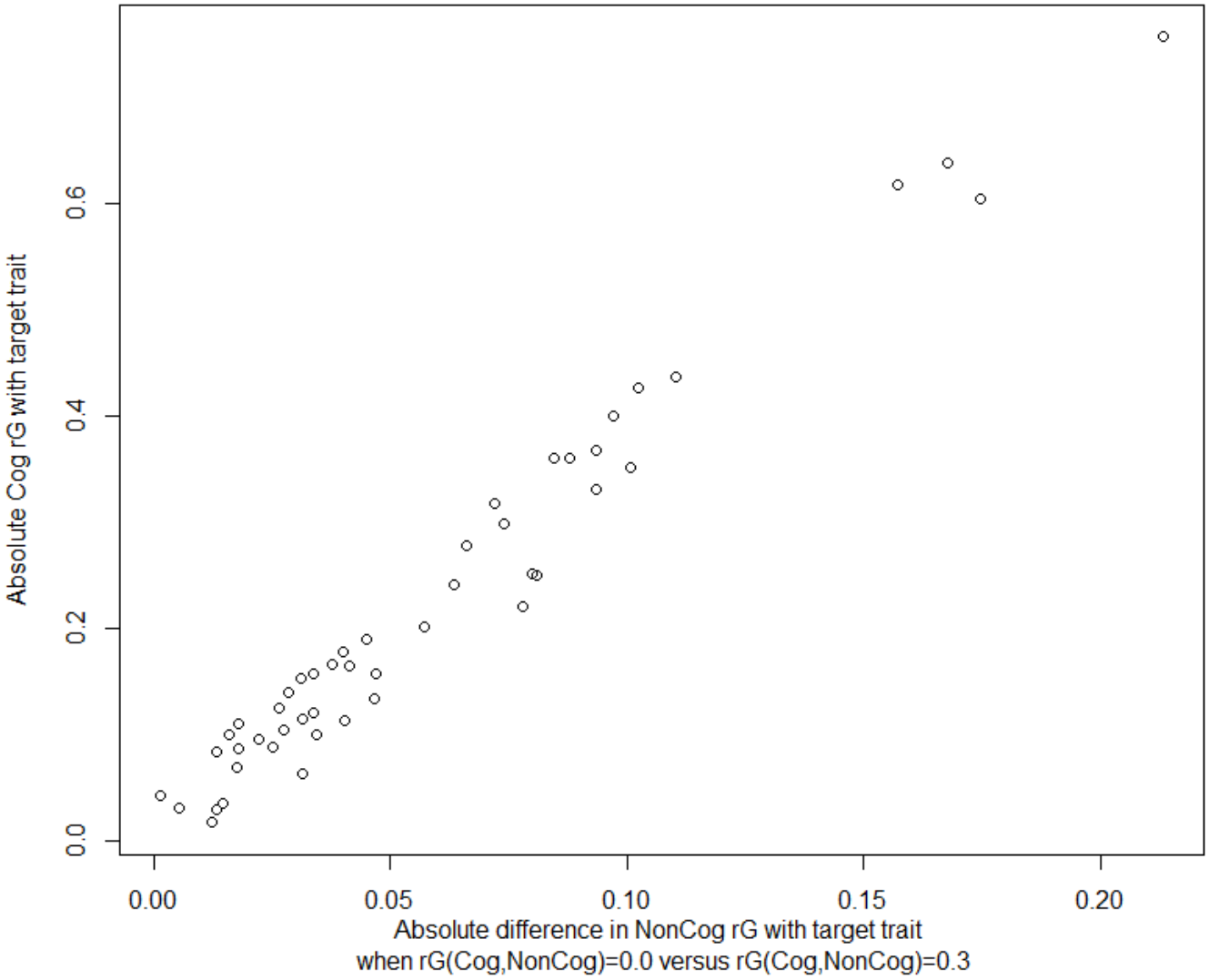


Supplementary Figure 5. Genetic correlations of Cog and NonCog with selected phenotypes, at different levels of Cog-NonCog correlation (rG).

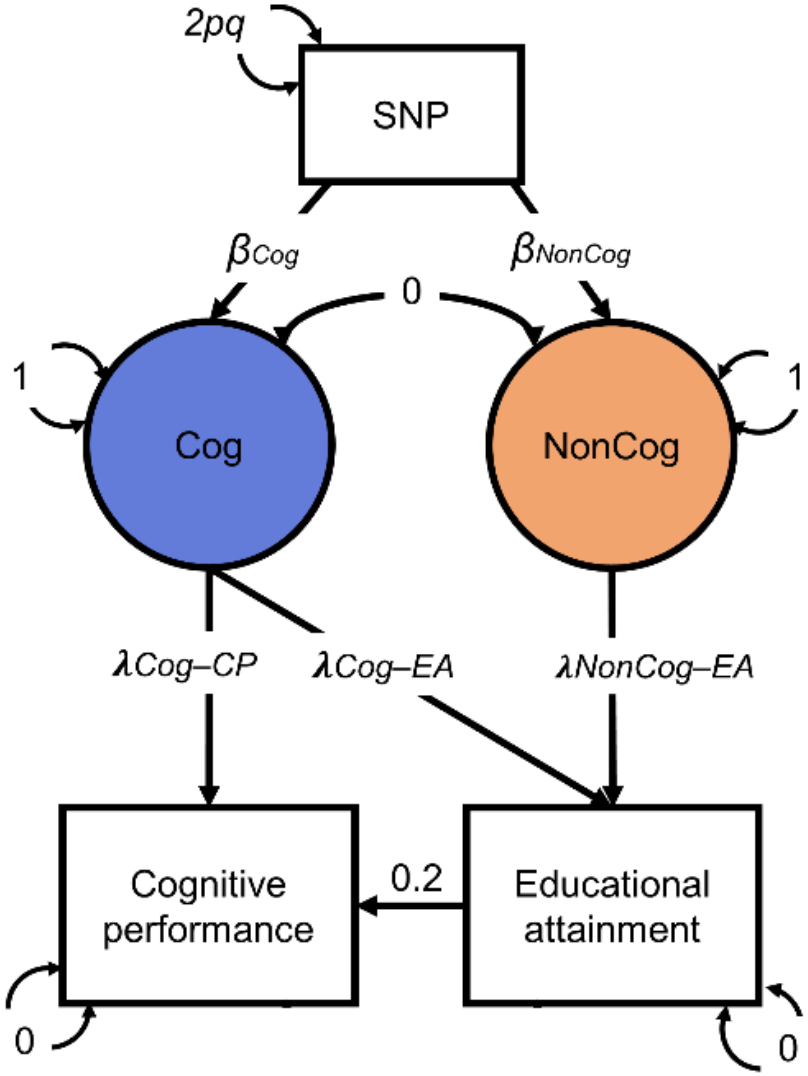
Genetic correlations of *NonCog* and *Cog* with selected phenotypes, as estimated with the model in **Supplementary Figure 17**. The dots represent genetic correlations estimated using Genomic SEM. Correlations with *NonCog* are in orange; with *Cog* in blue. The three panels present results depending on the correlation fixed between *NonCog* and *Cog*: 0, 0.1, 0.2 and 0.3. Error bars represent 95% CIs. Source GWAS are listed in **Supplementary Table 13**.

Supplementary Figure 6. Association of the difference in NonCog rG with target traits between Genomic SEM models and rGs of Cog with target traits.

On the x-axis we plot the absolute difference between the estimates of the genetic correlation with *NonCog* for traits when rG(*Cog*, *NonCog*) = 0 and when rG(*Cog*, *NonCog*) = 0.3. On the y-axis we plot the absolute estimate of the genetic correlation of Cog with all traits (identical for all rG(Cog,NonCog)). This figure shows that the differences across models in the genetic correlations of NonCog with target traits are bigger when the target traits have a stronger genetic correlation with Cog.

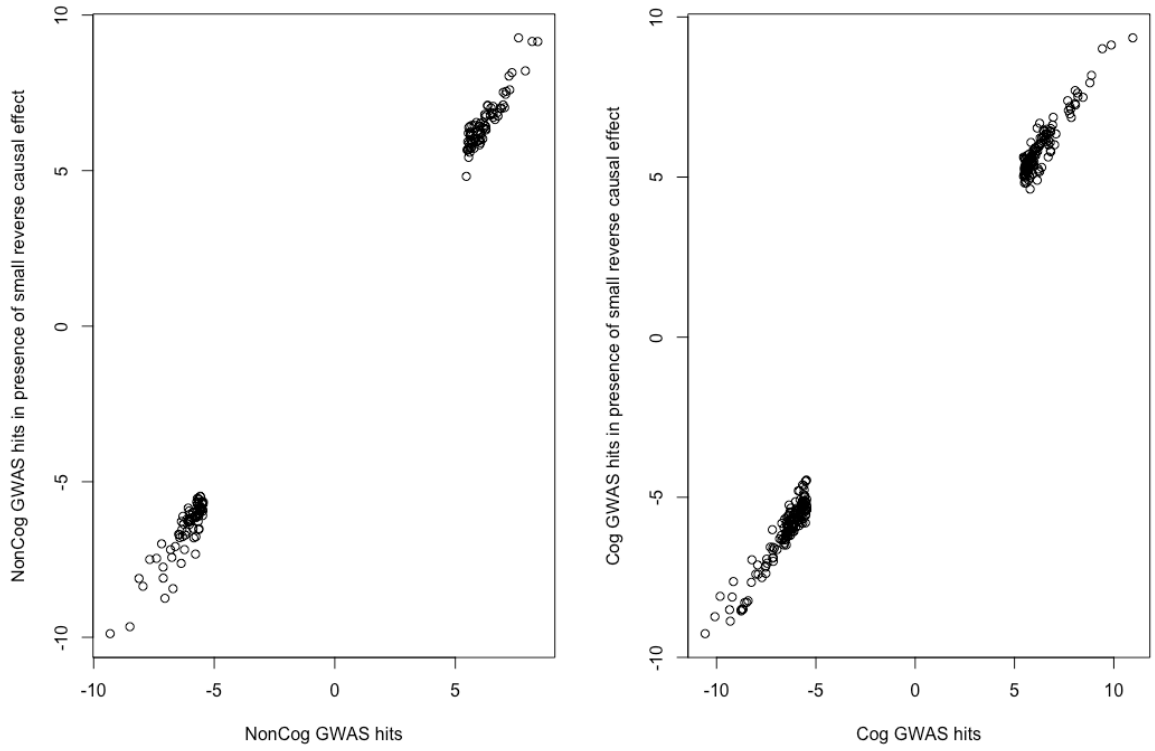


Supplementary Figure 7. Modified GWAS-by-subtraction model for Genomic SEM to allow a standardized effect of 0.2 of Educational Attainment on Cognitive Performance.

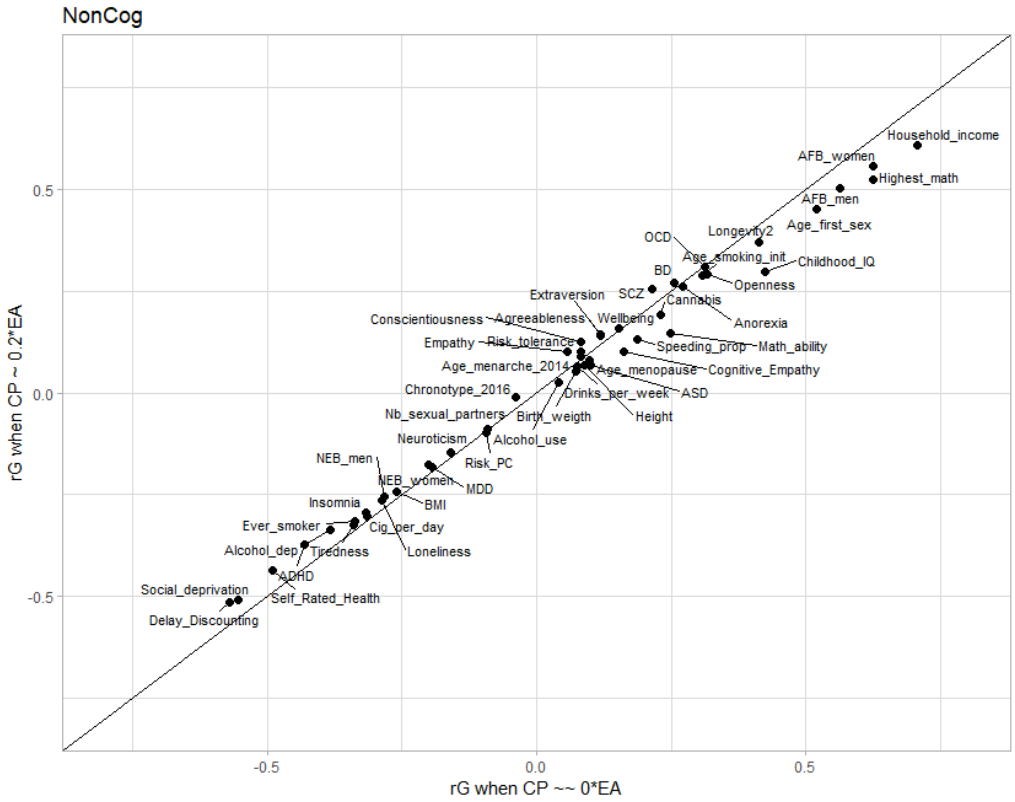


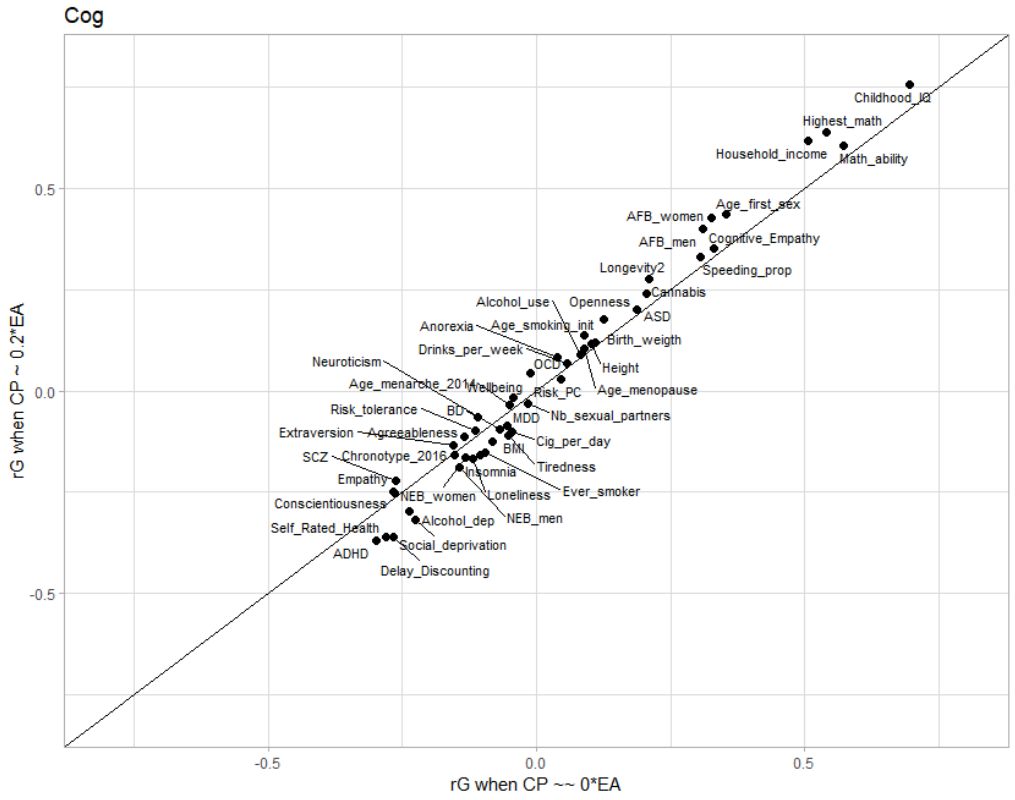
Supplementary Figure 8. Plot of the Z-statistics of the hits SNPs as estimated with our current GWAS-by-subtraction model (Figure 1) vs as estimated with a model allowing for an effect of EA on CP (Supplementary Figure 7) for Cog and for NonCog.

The SNPs whose the Z-statistics were estimated correspond to the independent genome-wide significant SNPS for Cog and NonCog respectively as found with model in Figure 1.



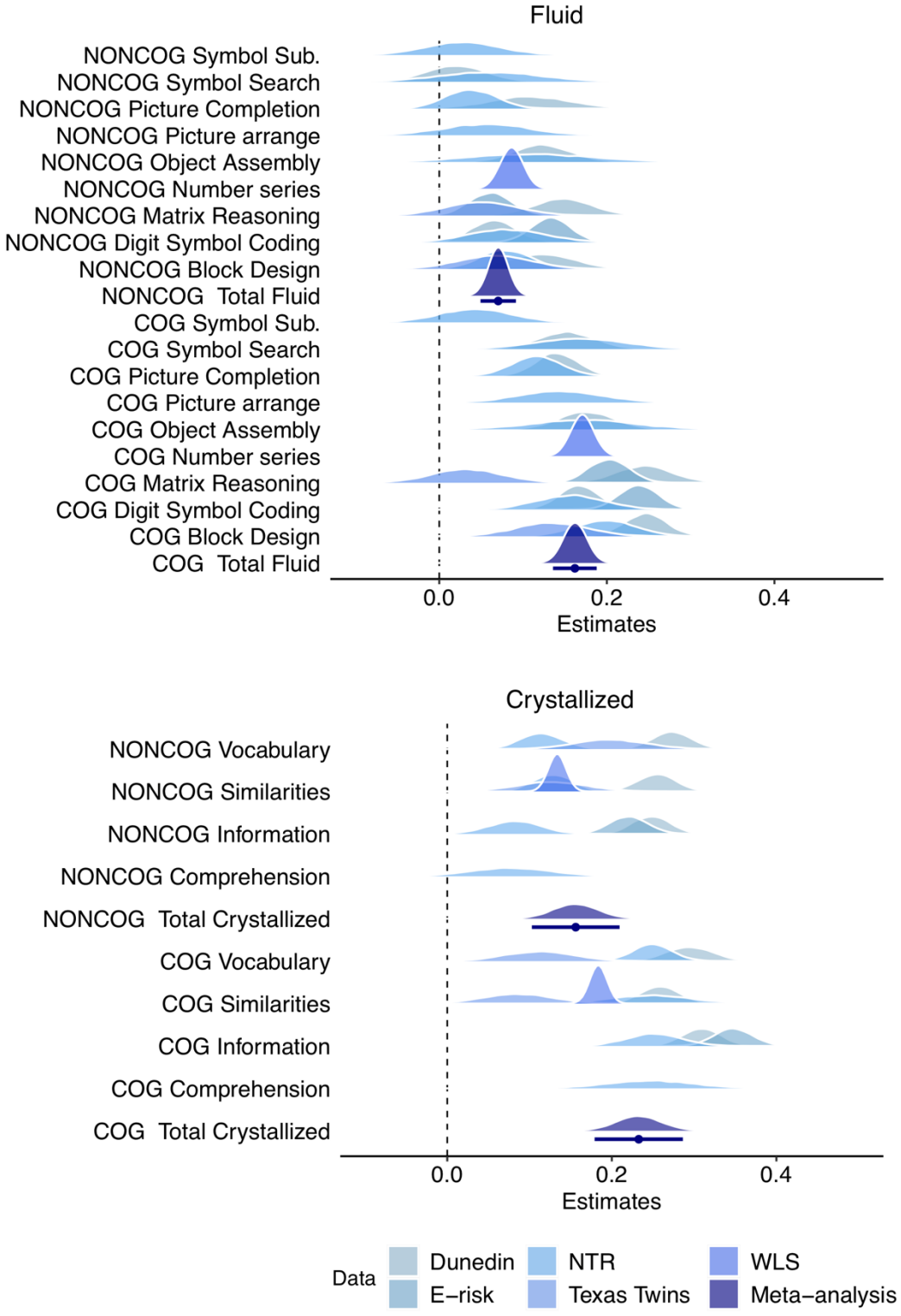
Supplementary Figure 9. Plot of the estimates of the genetic correlation of Cog and NonCog with selected phenotypes as estimated with the original GWAS-by-Subtraction model (x axis, Figure 1) versus as estimated with a model allowing for an effect of EA on CP (y axis, Supplementary Figure 7) for Cog and for NonCog.





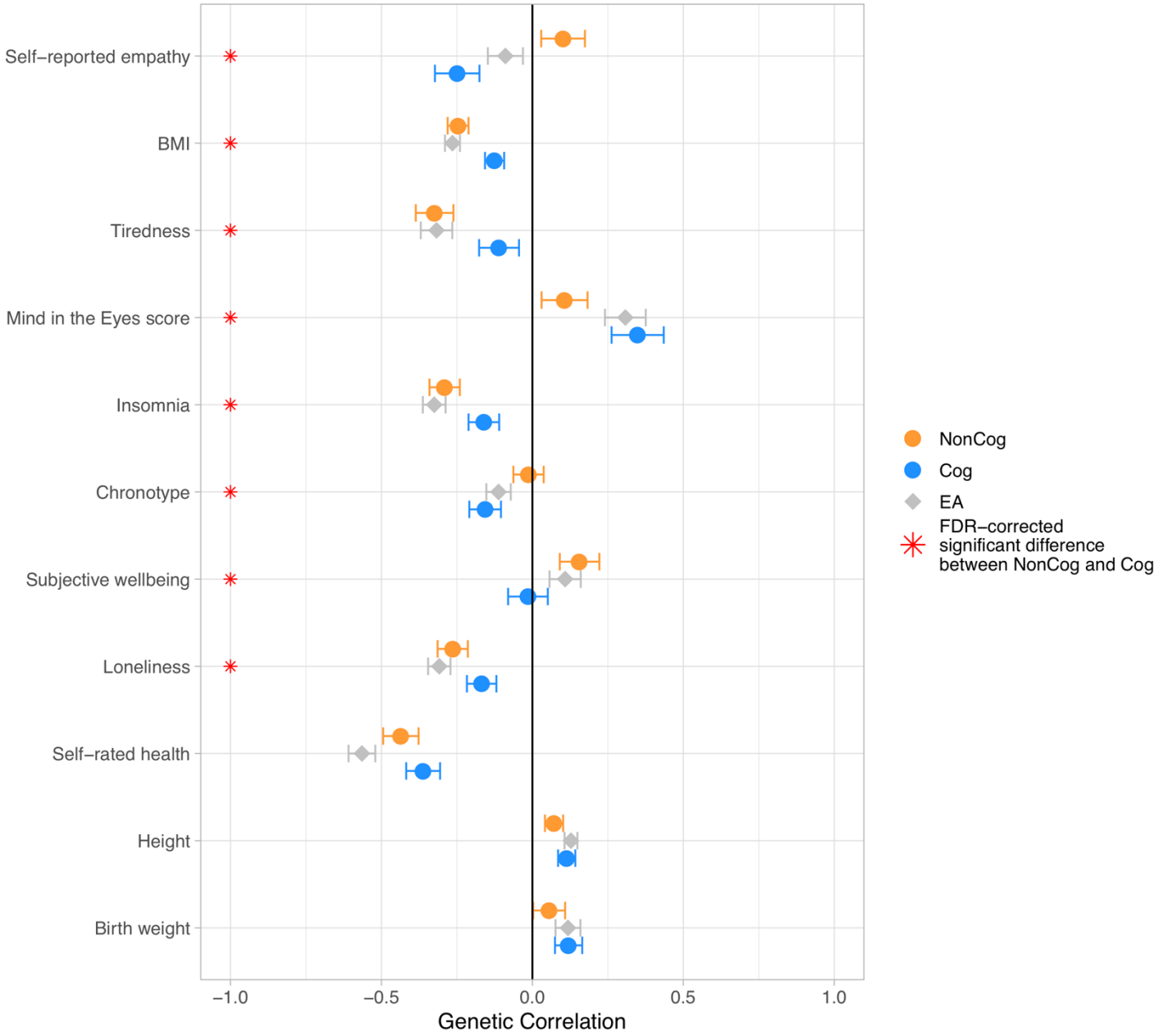
Supplementary Figure 10. PGS predictions of cognitive performance.

Meta-analytic estimates of the polygenic score associations with cognitive test performance. *Cog* and *NonCog* PRS were entered simultaneously in multiple regression. Results are ordered and meta-analysed separately for fluid (top panel) and crystalized (bottom panel) intelligence tests. The densities for individual tests were obtained by randomly generating normal distributions where the standardized regression estimate was included as the mean and the meta-analytic standard error as the standard deviation. In cases where measures had been collected in the same sample at multiple waves, the estimates were first meta-analysed within sample and the meta-analytic estimate and standard error were plotted. The densities in the darkest shade of blue, and the corresponding dots and error bars, show meta-analytic estimates and 95% confidence intervals across all tests of fluid and crystallized intelligence.



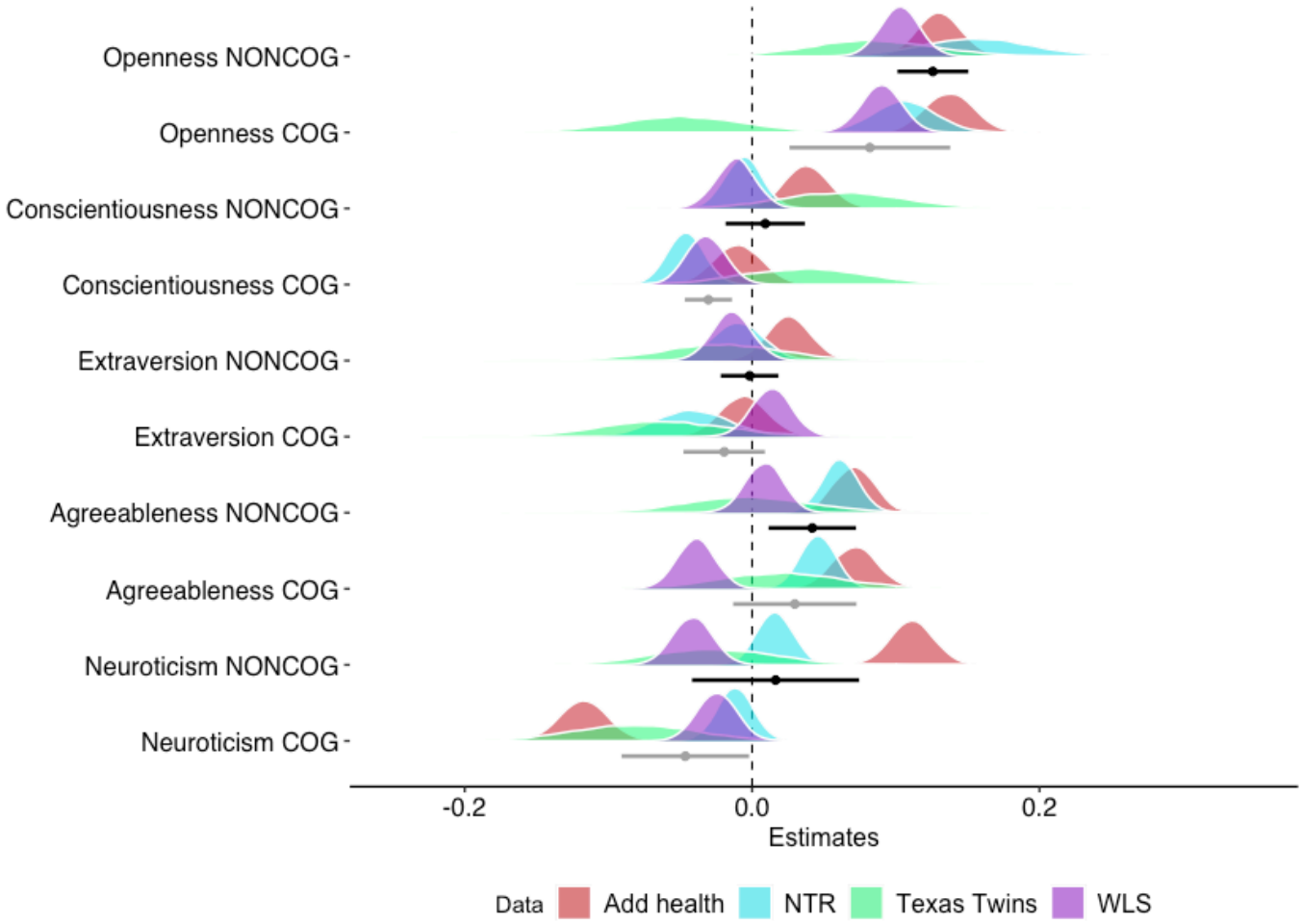
Supplementary Figure 11. Estimates of genetic correlations with *NonCog*, *Cog* and Educational Attainment (continuation).

Genetic correlations of *NonCog*, *Cog*, and EA with other selected phenotypes. The dots represent genetic correlations estimated using Genomic SEM. Correlations with *NonCog* are in orange; with *Cog* in blue; with EA in gray. Error bars represent 95% CIs. Red stars indicate a statistically significant (FDR corrected p-value < 0.05, two tailed test) difference in the magnitude of the correlation with *NonCog* versus *Cog*. The FDR correction was applied based on all genetic correlations tested (including in **Figure 4**). Exact p-values for all associations are reported in **Supplementary Table 14**.The difference test is based on a chi-squared test associated with a comparison between a model constraining these two correlations to be identical, versus a model where the correlations are freely estimated. Source GWAS are listed in **Supplementary Table 13**.



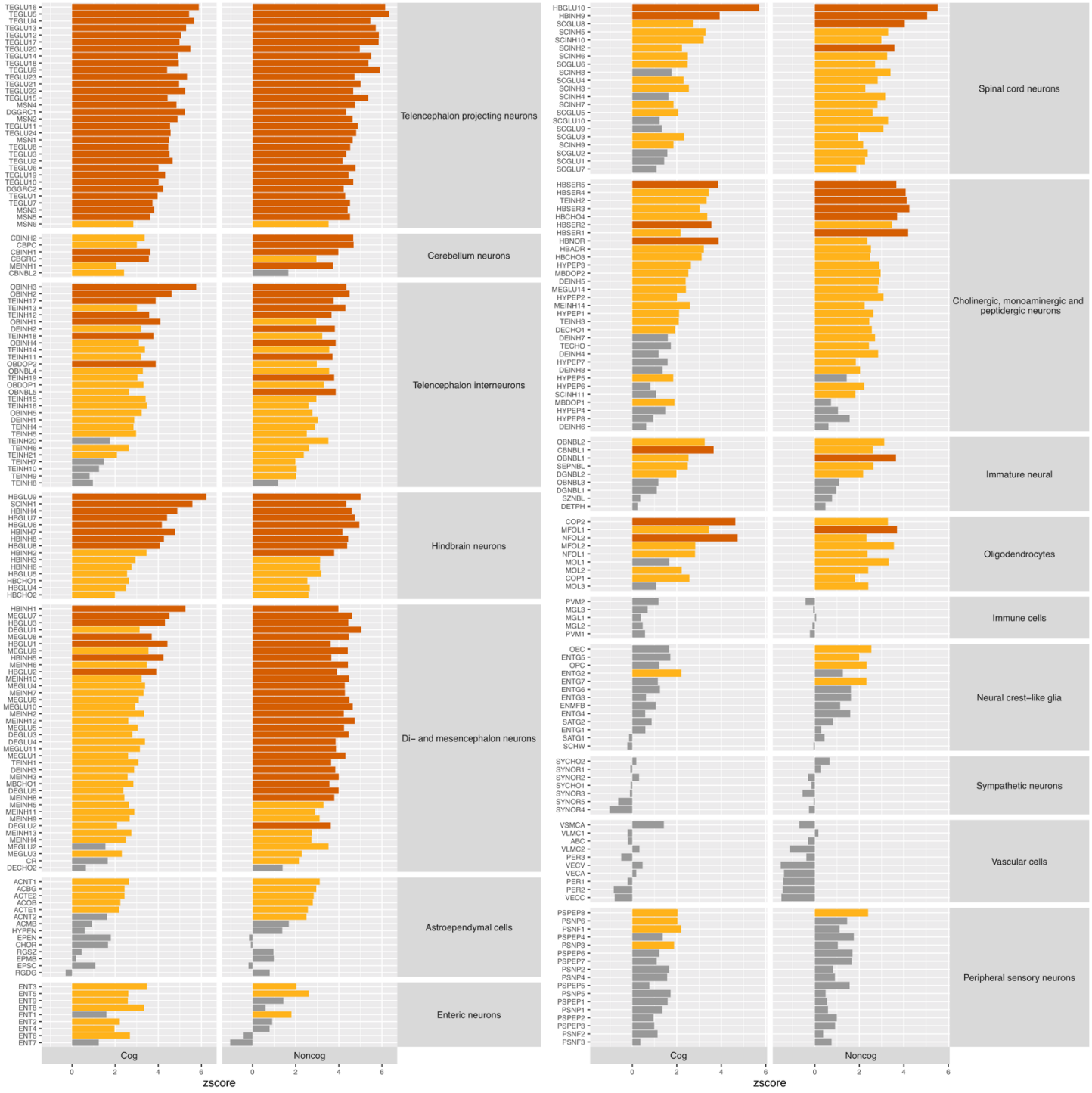
Supplementary Figure 12. PGS predictions of personality traits.

Meta-analytic estimates of the polygenic score associations with Big-5 personality traits. *Cog* and *NonCog* PRS were entered simultaneously in multiple regression. The densities for individual estimates were obtained by randomly generating normal distributions where the standardized regression estimate was included as the mean and the standard error as the standard deviation. In cases where measures had been collected in the same sample at multiple waves, the estimates were first meta-analysed within sample and the meta-analytic estimate and standard error were plotted. Black and grey points represent meta-analytic estimates and the width of each band represents 95% CI.

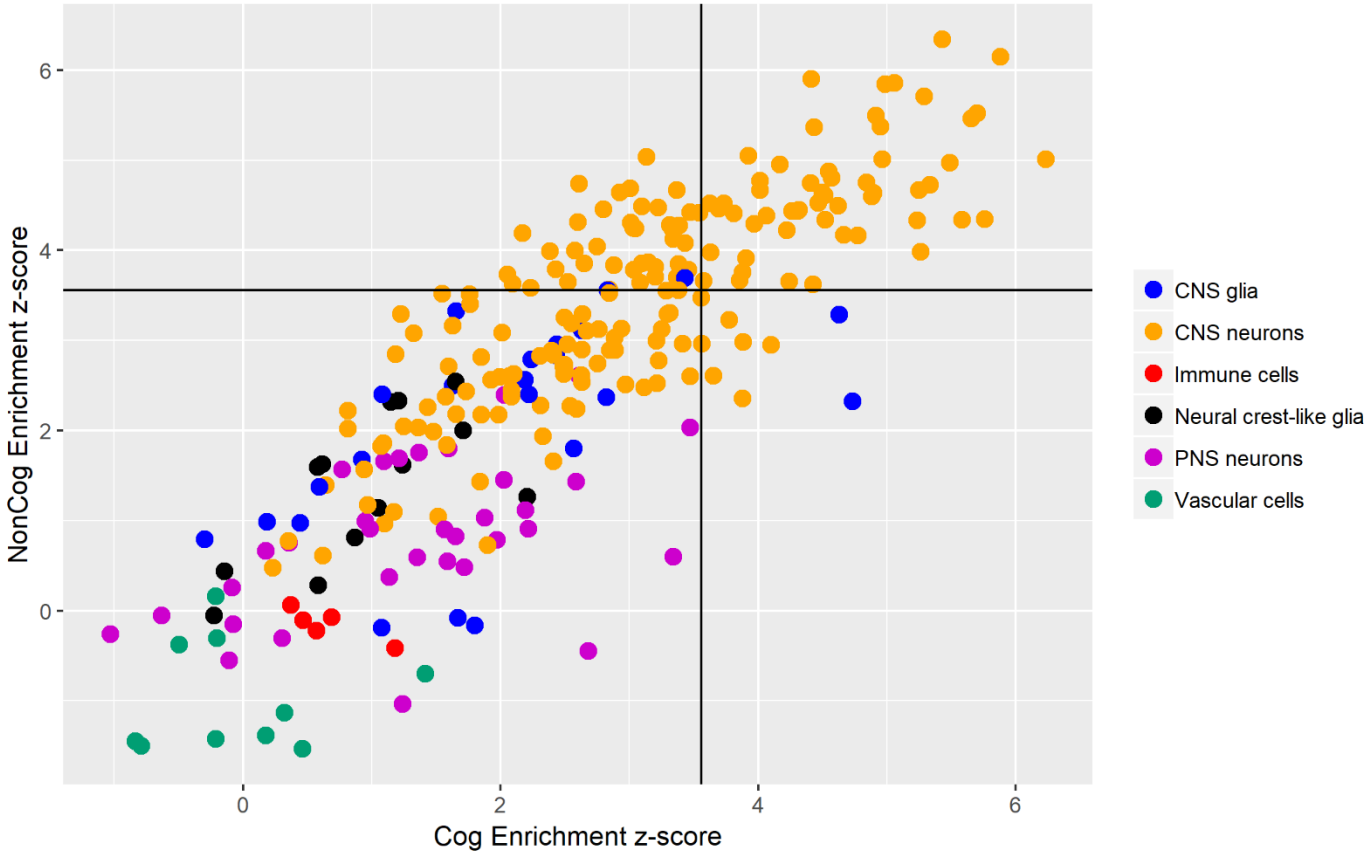


Supplementary Figure 13. Z-statistics of enrichment of *Cog* and *NonCog* for 265 cell-types computed with MAGMA.

Categories of the nervous system cell-types are defined following Taxonomy 2 (**Supplementary Table 17**). Associations significant after FDR correction are represented in orange, in red if significant after Bonferroni correction.



Supplementary Figure 14. Plot of MAGMA cell-types enrichment z-statistics of *Cog* vs *NonCog*.
Cell-types are categorized following Taxonomy 1 (**Supplementary Table 17**). Black lines represent significant thresholds with Bonferroni correction.

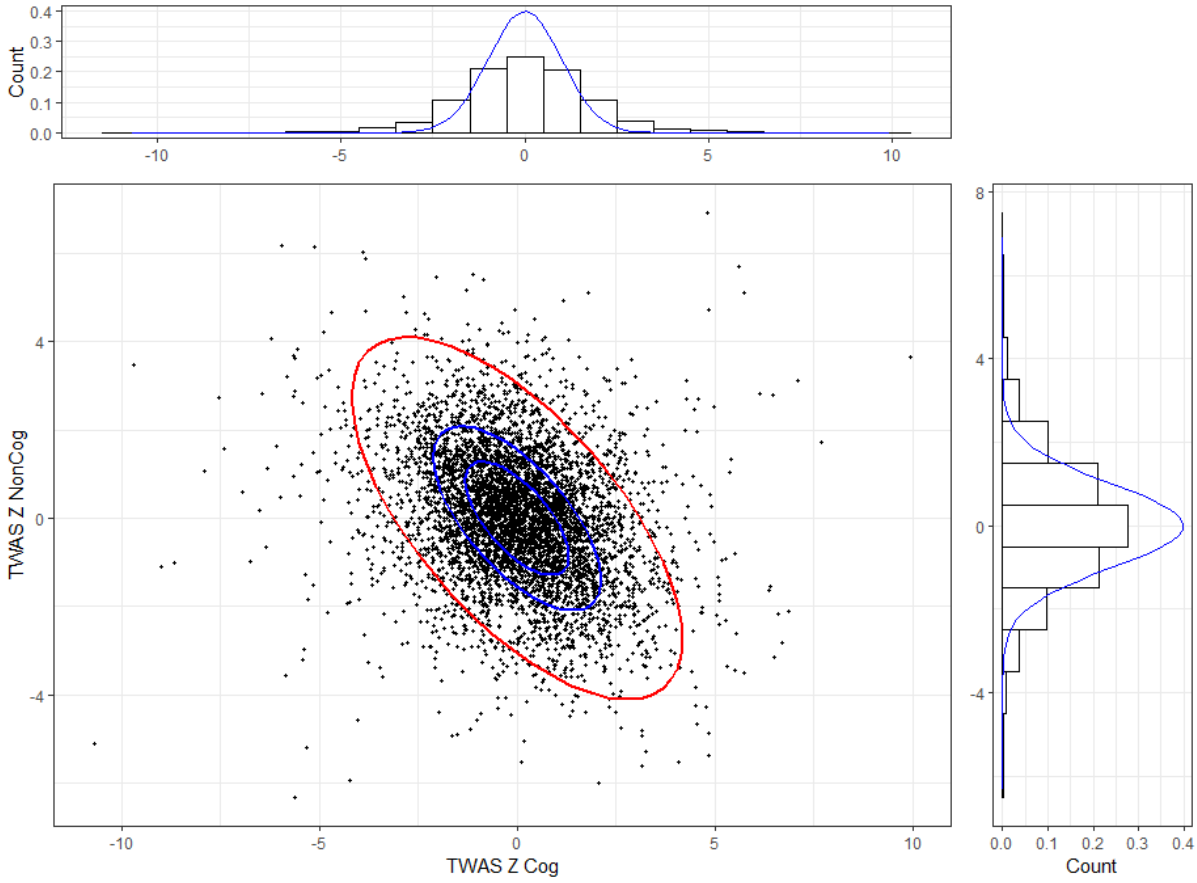


Supplementary Figure 15. Z-statistics of enrichment of Cog and NonCog for 265 cell-types computed with stratified LDSC regression.

Categories of the nervous system cell-types are defined following Taxonomy 2 (**Supplementary Table 17**). Associations significant after FDR correction are represented in orange, in red if significant after Bonferroni correction.

Supplementary Figure 16. Scatterplot of TWAS Z-statistics for *NonCog* and *Cog*.

The figure shows a scatterplot of gene-transcript test-statistics from TWAS of *NonCog* against test-statistics from TWAS of *Cog*. The histograms along X and Y axes show distributions of test-statistics for all genes included in the TWAS, with overline of the standard normal distribution in blue. Because of GWAS sample overlap and the joint estimation of *NonCog* and *Cog* effects within the same model, the summary statistics of these GWAS are not independent (LD-score cross-trait intercept for *NonCog* and *Cog* = -0.67), see **Supplementary Note**. In the plot, the blue ellipses represent the 68% and 95% CIs (based on the bivariate null-distribution of test-statistics expected given the LD-score intercept). The red ellipse represents the gene wide significance level of this bivariate null distribution ($p < 0.05/N$ genes): Genes outside of this ellipse show evidence either of concordant or discordant association with *NonCog* and *Cog*.



Supplementary Figure 17. Genetic correlation using Genomic SEM without SNP effects.

Genomic SEM model used to directly estimate the covariance between *Cog* and *NonCog* and a third trait, without the need to first perform a *Cog* and *NonCog* GWAS. The covariance of EA and a tertiary trait explained by *NonCog* is calculated as ENC = λNonCog-EA * λNonCog-LatentTrait * λTrait. The covariance between EA and a tertiary trait explained by *Cog* is calculated as EC = λCog-EA * λCog-LatentTrait * λTrait. The total covariance between EA and a tertiary trait is calculated as Etotal = λNonCog-EA * λNonCog-LatentTrait * λTrait + λCog-EA * λCog-LatentTrait * λTrait. The percentage of the genetic covariance explained by *NonCog* was ENC/Etotal and the percentage explained by *Cog* was defined as EC/Etotal. This analysis only yields valid results for trait where ENC and EC are both positive or both negative.