July 20, 2020

Supplementary Information for:
A General Dimension of Genetic Sharing Across Diverse Cognitive Traits Inferred from Molecular Data

Javier de la Fuente, Gail Davies, Andrew D. Grotzinger, Elliot M. Tucker-Drob* & Ian J. Deary*

*Correspondence to: tuckerdrob@utexas.edu or i.deary@ed.ac.uk

This PDF file includes:

Other Supplementary Materials for this manuscript include the following:

Supplementary Tables 7 – 30 (Excel file)

Supplementary Methods

Interpreting the Heterogeneity Statistic

Here we provide a description of what the Genomic SEM heterogeneity statistic (Q) indexes, and how we can appropriately interpret the detected heterogeneity by investigating the univariate GWAS results for the individual phenotypes.

Q indexes the extent to which model misfit occurs for a *common pathway* model in which the effects of a given SNP on the individual phenotypes are specified to occur exclusively via a single effect of the SNP on the latent factor (Supplementary Figure 9, left panel) compared to a less restrictive *independent pathways model* in which the effects of a given SNP on the individual phenotypes are specified to occur directly on those phenotypes (Supplementary Figure 9, right panel). In other words, low Q indicates that the SNP plausibly acts on the latent factor, whereas high Q indicates that the SNP does not plausibly act on the latent factor.

Under the *common pathway* model, the expected SNP effects ($\hat{b}_{SNPm,yk}$) on phenotype *k*, is $b_{SNPm,F} \times \lambda_k$, i.e.:

$$\begin{bmatrix} \hat{b}_{SNPm,y1} \\ \hat{b}_{SNPm,y2} \\ \hat{b}_{SNPm,y3} \\ \hat{b}_{SNPm,y4} \\ \vdots \\ \hat{b}_{SNPm,yk} \end{bmatrix} = b_{SNPm,F} \begin{bmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \\ \lambda_4 \\ \vdots \\ \lambda_k \end{bmatrix}. \qquad \text{(Equation S1)}$$

Misfit occurs when the vector of expected SNP effects on phenotypes 1 through *k* deviates from the vector of observed SNP effects on phenotypes 1 though *k* ($b_{SNPm,yk}$), as estimated from the univariate GWASs. If the effects of the SNP on the individual phenotypes occur exclusively by way of the effect of the SNP on the common factor, the vector of observed SNP effects should be proportional to the vector of unstandardized loadings of those phenotypes on the common factor, and Q will be low. If, however, the vector of observed SNP effects is not proportional to the vector of unstandardized loadings of those phenotypes on the common factor, Q will be high, and a model in which the SNP effects on the phenotypes occur exclusively via the common factor will be rejected.

When Q is high for a given SNP, the linear association between the vector of univariate regression coefficients, $b_{SNPm,yk}$, and the vector of unstandardized factor loadings, λ_k, will be weaker, and there may be one or more outliers. Note that we do not necessarily expect that a SNP that acts

exclusively on the common factor to have relatively equal univariate associations with each phenotype (this will only occur if the factor loadings are all relatively similar). Rather, if the SNP acts exclusively on the common factor, we expect the univariate associations to scale with the unstandardized factor loadings for the corresponding phenotypes. For instance consider a phenotype with a relatively low unstandardized factor loading. We expect that a SNP that acts directly and exclusively on the common factor to have a relatively lower association with that phenotype compared to its associations with the other phenotypes. In fact, if the association with that phenotype is comparable to the association of that SNP with other phenotypes, Q will be high.

We next explain why it is the SNP's beta coefficients, and not its Z statistics or p values, that must be explored to investigate heterogeneity. Importantly, when the different phenotypes differ dramatically in their sample sizes, SNP heritabilities, or polygenicity, the Z statistics (or p value, which is derived from the Z statistic) for a given SNP and each phenotype are *not* expected to be proportional to the magnitude of the unstandardized factor loadings for those phenotypes. For instance, imagine a scenario in which Q is 0 (no heterogeneity) for a particularly SNP, such that the correlation between the vectors of betas and factor loading is 1.0. We would still likely see differences in Z statistics (and p values) across phenotypes that do not correspond with their unstandardized factor loadings. All else being equal, the phenotypes with the largest Ns will have very high Z statistics and those with the smallest Ns will have very low Z statistics (and may not be significant). If we investigate the Z statistics or p values, we may incorrectly infer that the SNP is relevant to the high N phenotypes but not the low N phenotypes. However, if we investigate the betas and rely on the Q statistic, we will come to a very different (and more correct) conclusion. If Q is 0 (such that the method of correlated vectors produces r=1.0), and the SNP effect on the common is genome-wide significant, we will correctly conclude that we have identified a SNP that plausibly acts on the phenotypes via the factor.

Now consider what happens when Q is high for a particular SNP. We may be interested in identifying the source(s) of the heterogeneity across phenotypes. The same principles as above hold; we must investigate the betas. If we investigate the Z statistics or p values, we will simply conclude that the SNP is specific to the phenotypes for which the univariate GWASs are more highly powered, whether this is true or not.

Next, we consider how these principles apply to the results with respect to genetic *g*. Table S30 provides the univariate GWAS summary statistics for the lead SNPs from the 3 loci that are genome-wide significant for both Q and genetic *g*.

The first hit considered is for a lead SNP within the APOE gene, which is a well-known risk factor for Alzheimer's Disease. Supplementary Figure 10 is the scatterplot of the betas against the

unstandardized factor loadings. It can be seen that the betas correspond very closely to the factor loadings for all traits except VNR, which is a test that does not decline with age. The betas for memory and RT are also low, but these are traits with relatively lower unstandardized loadings, so these observations are unlikely to contribute directly to high Q. VNR is an outlier because its beta is low relative to its factor loading. Note that only Symbol Digit and Trails-B pass the genome-wide significance threshold, so one (likely incorrect) interpretation would be that this is a SNP that is only relevant to those two traits. However, remember that Q is examining heterogeneity in betas across all traits (not just the significant ones), and whether they scale with factor loadings. If our goal was to tally the intersection of univariate hits for the same SNPs across traits, we would not need multivariate methods. However, our goal is to evaluate how these SNPs operate within a formal multivariate model. Importantly, Q is genome-wide significant for this SNP, which is why we investigate it further. However, differences in the significance of the SNP associations for the individual traits are not directly relevant for interpreting the genome-wide significant Q statistic.

The second hit considered is for a lead SNP within a locus on Chromosome 17. Supplementary Figure 11 is the scatterplot of the betas against the factor loadings. It can be seen that there is not much correspondence between the factor loadings and the SNP effects, even with outliers removed. The SNP has its strongest association with RT (a measure of psychomotor speed), but it also has a sizable association with Symbol Digit. The RT association is the only genome-wide significant univariate association for this SNP, but one hesitates to conclude that this is a SNP that is specific to RT, given the magnitude of the Digit Symbol beta. A more conservative conclusion would be that this is a SNP that is more broadly related to speeded abilities.

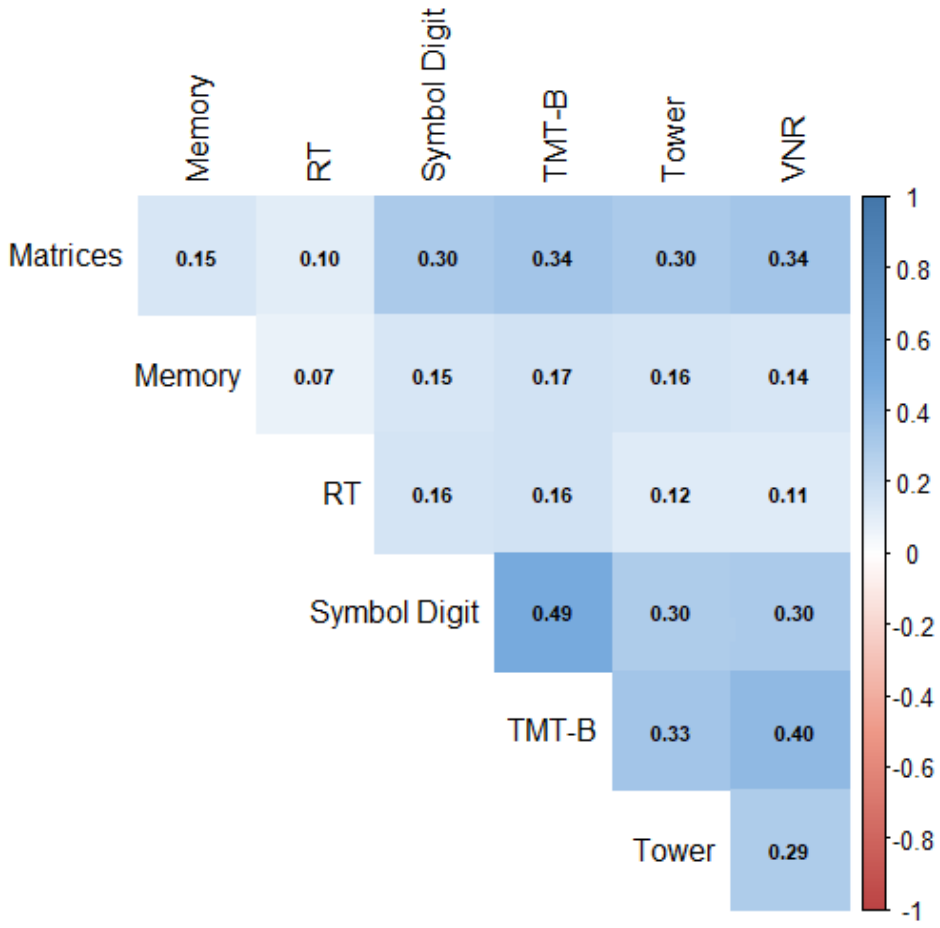
The last hit considered is for a lead SNP within a locus on Chromosome 3. Supplementary Figure 12 is the scatterplot of the betas against the factor loadings. First, it is important to observe that although there appears to be good correspondence between the factor loadings and the betas, this isn't exactly the case, as two of the betas are slightly negative. Because the factor loadings are all positive, it is not possible for a vector that contains both positive and negative SNP effects to be proportional to the factor loadings. Rather, there appears to be two clusters of SNP effects. One cluster (Memory, RT, and Digit Symbol; all tests of basic mental processes) is characterized by associations that are very close to 0. A second cluster (Trails-B, Tower, Matrices, VNR; all tests of higher order cognition) is characterized by similarly sized positive associations. This SNP only exhibits Z statistics surpassing the suggestive threshold ($p<1\times10^{-5}$) for Trails-B and VNR, but in fact the SNP's beta coefficient for Tower is larger (.029) than its coefficient for Trails-B (.023). Tower (n = 11,263) is simply less well powered than is Trails-B (n = 78,547). One would be very hesitant to say that this SNP is only relevant for Trails–B and

VNR as its regression relations with Tower and Matrices are very similar in magnitude as those for Trails–B and VNR. One sensible interpretation of this pattern is that that this SNP is relevant for higher-order cognition, but not basic cognitive processes.

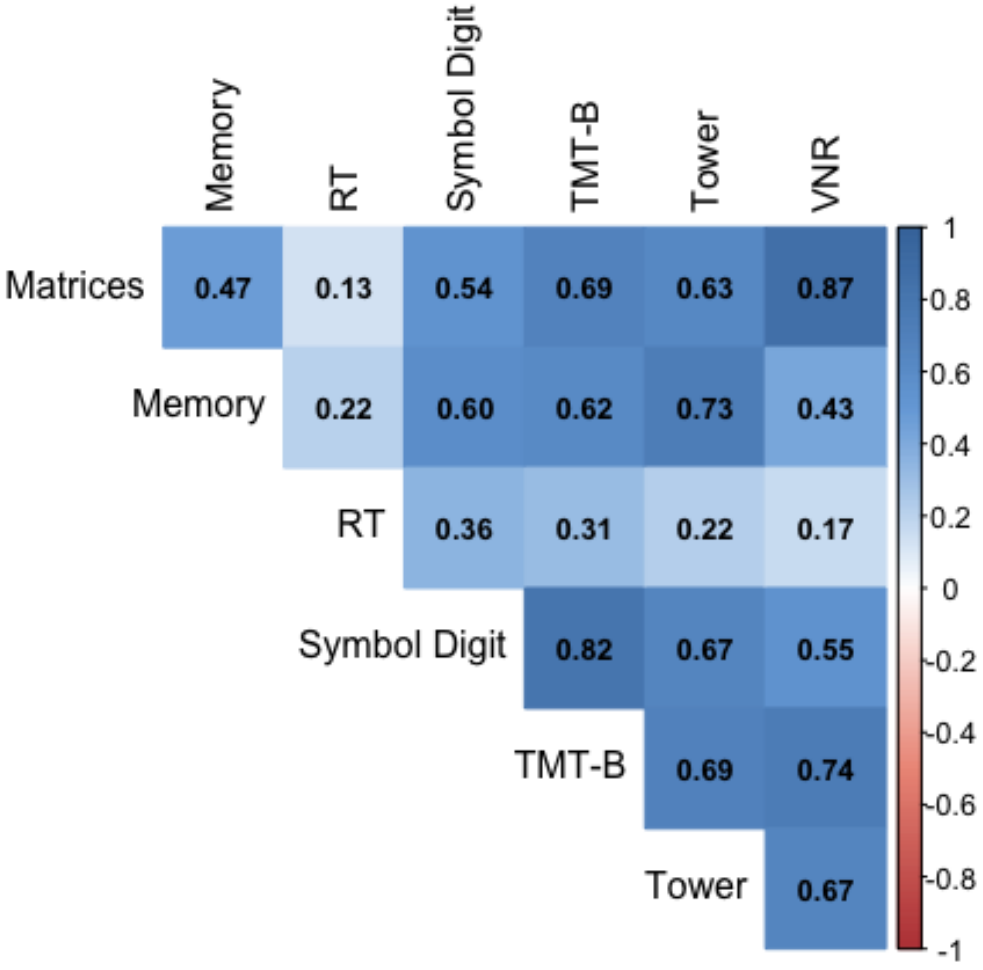
Some points of caution are important to keep in mind. First, the formal hypothesis being tested, for which a genome-wide multiple testing correction is made, is the omnibus test of heterogeneity (Q). Interpretation of the specific pattern of SNP-phenotype associations following identification of genome-wide significant Q loci is post-hoc, and should therefore be considered tentative. Nevertheless, for the reasons described above, basing such investigation of the individual phenotype associations on regression coefficients is more appropriate than basing such investigations on Z-statistics or p-values. This is because Genomic SEM is a formal framework for modeling effect sizes across traits, and is not simply a method of pooling p values. Importantly, interpreting genome-wide significant Q loci in terms of on p values or Z statistics from disproportionally powered univariate GWASs can lead to interpretations that fail to account for the fact that "the difference between significant and not significant is [not necessarily] itself significant"[1].

Second, overfitting is always bound to be a problem when SNPs are identified on the basis of surpassing a stringent significance threshold for their associations. In conventional univariate GWAS it is well-known that the effect sizes for genome-wide significant SNPs are likely to be overestimated in the discovery sample. In multivariate GWAS, such as the analyses conducted on genetic *g*, when SNPs are identified on the basis of surpassing a stringent threshold for heterogeneity, there is likely to be collider bias that builds in artifactual dependencies between individual SNP effect sizes. Short of having well-powered independent validation data to re-estimate individual SNP effects for Q hits, this collider bias will be difficult to fully resolve, and must be considered when making interpretations.

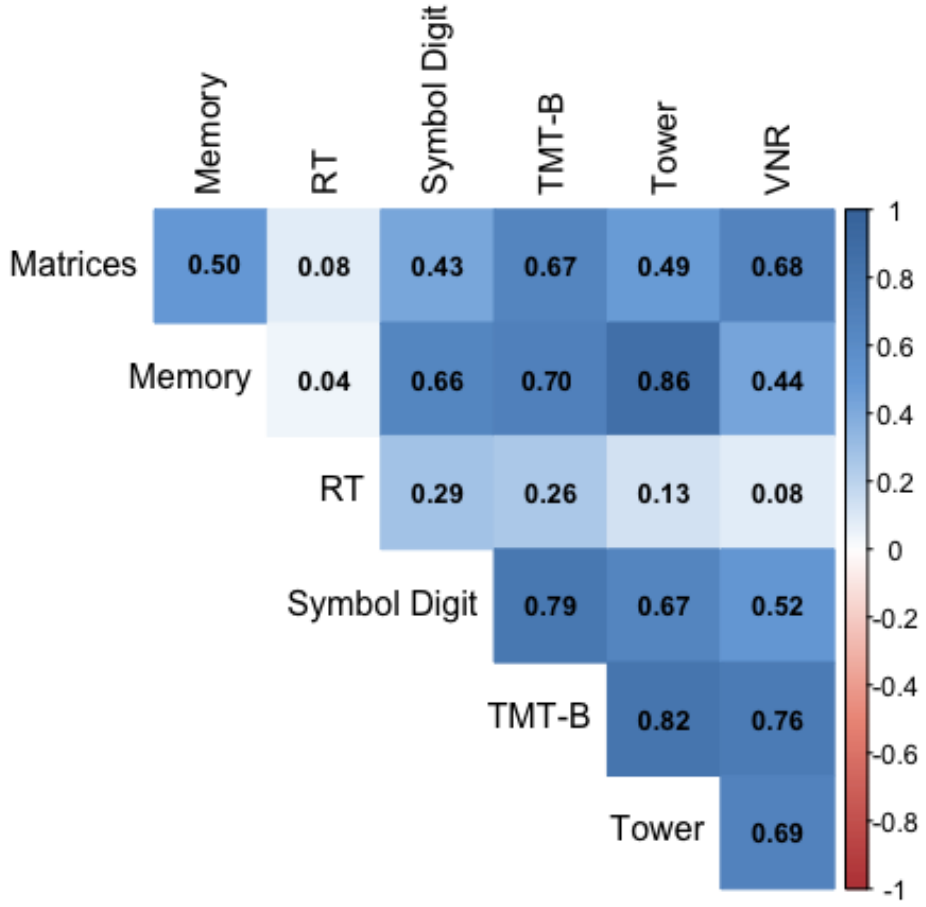
Supplementary Figure 1. Hierarchical structure of intelligence differences (adapted from Deary[2], cf. Carroll[3] and Tucker-Drob[4]). Cognitive abilities composing intelligence are measured via a variety of diverse cognitive tests (Level 1). Spearman[5,6] discovered that person-to-person differences in performance on many different cognitive tests are moderately positively correlated. Later work refined this discovery[3,7–10], and articulated the hierarchical model, after observing particularly strong positive correlations among tests within cognitive domains (Level 2), such that latent traits representing the domains of performance can be extracted to represent their common variance. People who have strengths in one domain also tend to have strengths in other domains, such that a general intelligence factor, *g,* can be extracted (Level 3). This hierarchical structure of intelligence differences is well-established[3]. Approximately 25-50% of the variation in performance on the individual tests of a diverse cognitive battery is accounted for by *g,* with additional variation accounted for by the cognitive domains after taking *g* into account, and additional variance explained by factors that are specific to the individual tests and by measurement error. When only one test per domain is available, the sources of variation stemming from levels 1 and 2 to cannot be separated, but *g* can still be extracted. It has been found that, so long as the tests used to measure cognitive abilities are sufficiently diverse, almost the same *g* factor is always extracted[6,11].



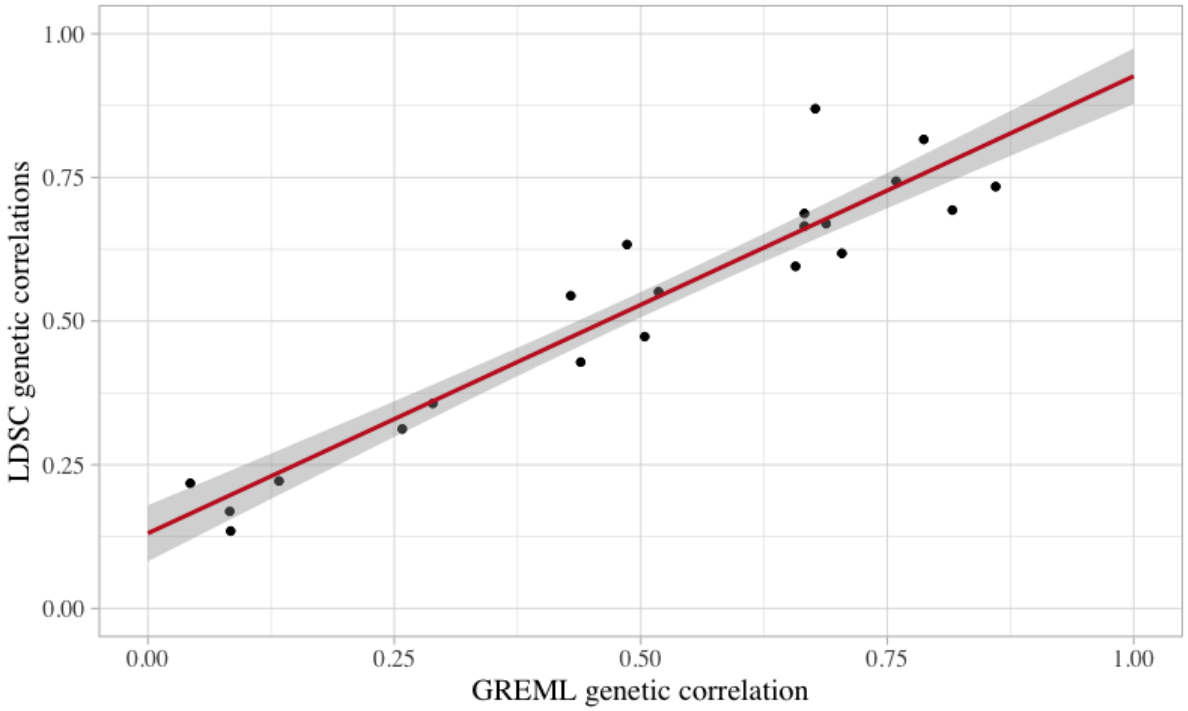
Supplementary Figure 2. Heat-map of phenotypic correlations among the seven UK Biobank cognitive tests. Matrix = Matrix Pattern Completion task; Memory = Memory – Pairs Matching Test; RT = Reaction Time; Symbol Digit = Symbol Digit Substitution Task; Trails-B = Trail Making Test – B; Tower = Tower Rearranging Task; VNR = Verbal Numerical Reasoning Test. All cognitive tests were first residualized for age and several other covariates (see Method).



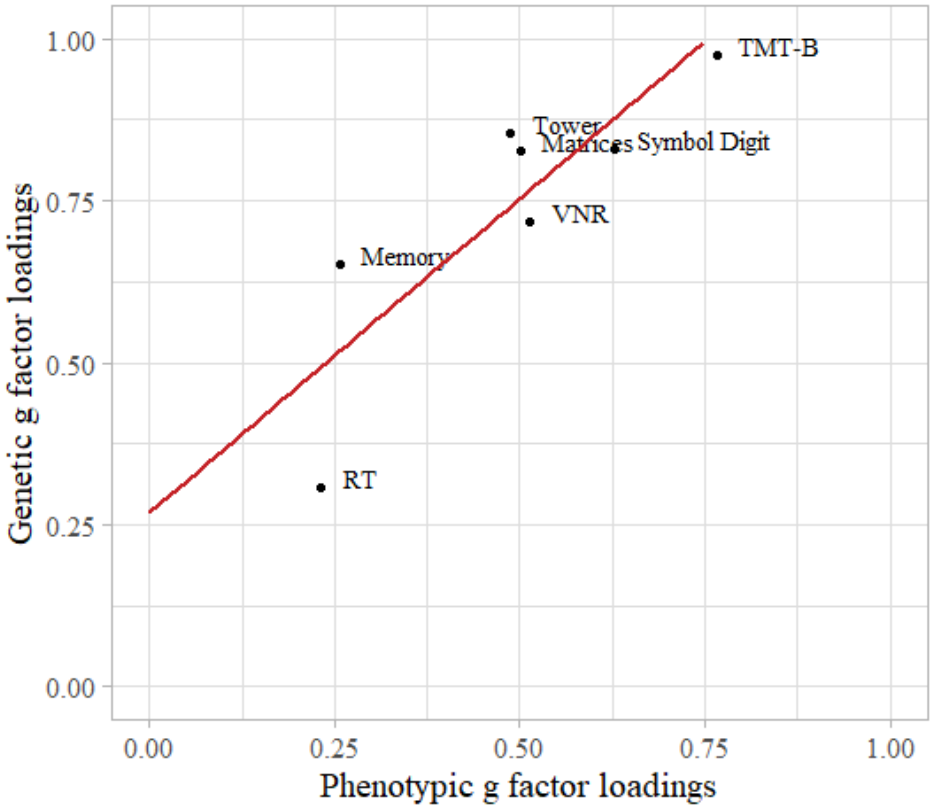
Supplementary Figure 3. Heat-map of LDSC-estimated genetic correlations among the seven UK Biobank cognitive phenotypes. Matrix = Matrix Pattern Completion task; Memory = Memory – Pairs Matching Test; RT = Reaction Time; Symbol Digit = Symbol Digit Substitution Task; Trails-B = Trail Making Test – B; Tower = Tower Rearranging Task; VNR = Verbal Numerical Reasoning Test.



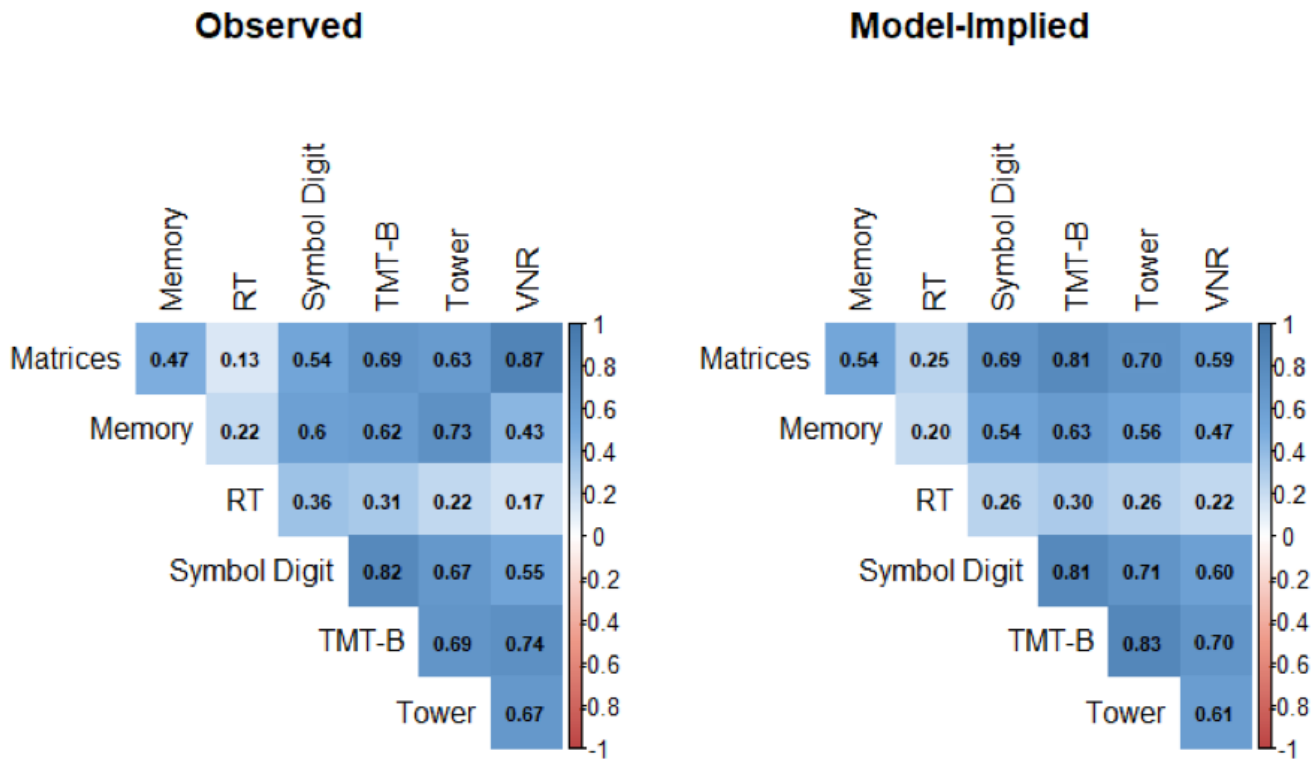
Supplementary Figure 4. Heat-map of GREML-estimated genetic correlations among the UK Biobank cognitive phenotypes. Matrix = Matrix Pattern Completion task; Memory = Memory – Pairs Matching Test; RT = Reaction Time; Symbol Digit = Symbol Digit Substitution Task; Trails-B = Trail Making Test – B; Tower = Tower Rearranging Task; VNR = Verbal Numerical Reasoning Test.



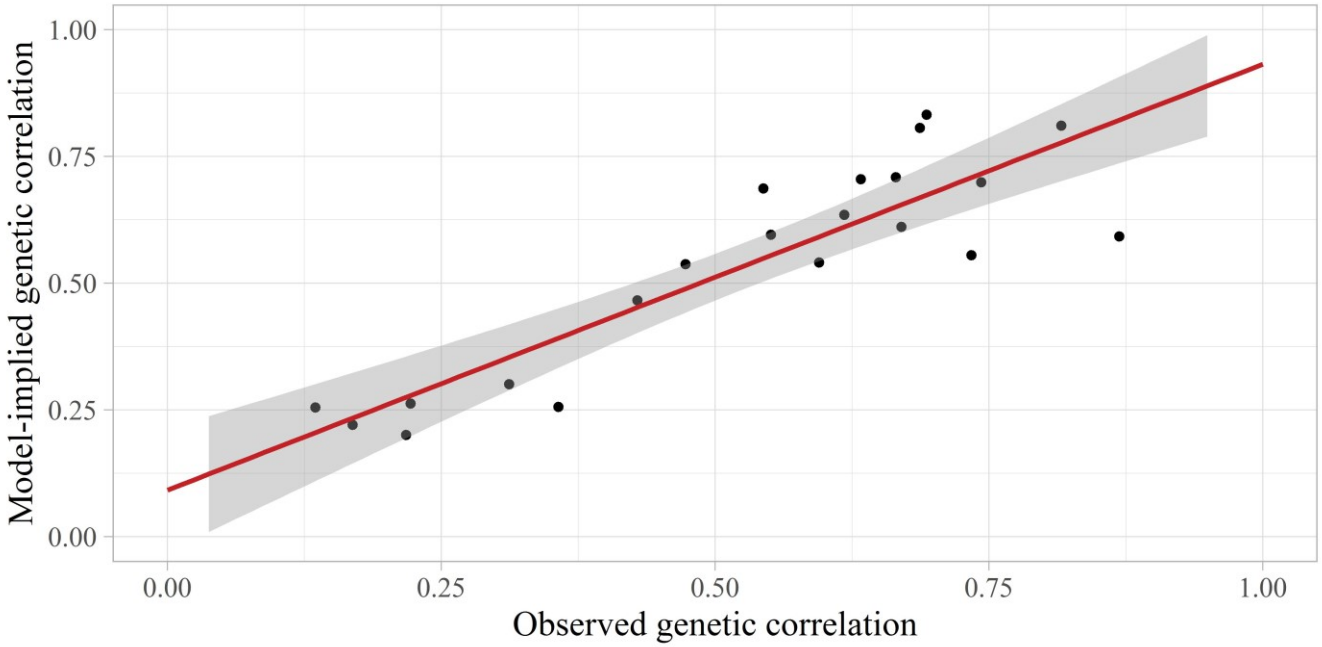
Supplementary Figure 5. Scatterplot of LDSC and GREML genetic correlations (from Figs S2 and S3) among UK Biobank cognitive phenotypes. Note: Shaded area represents 95% confidence interval.



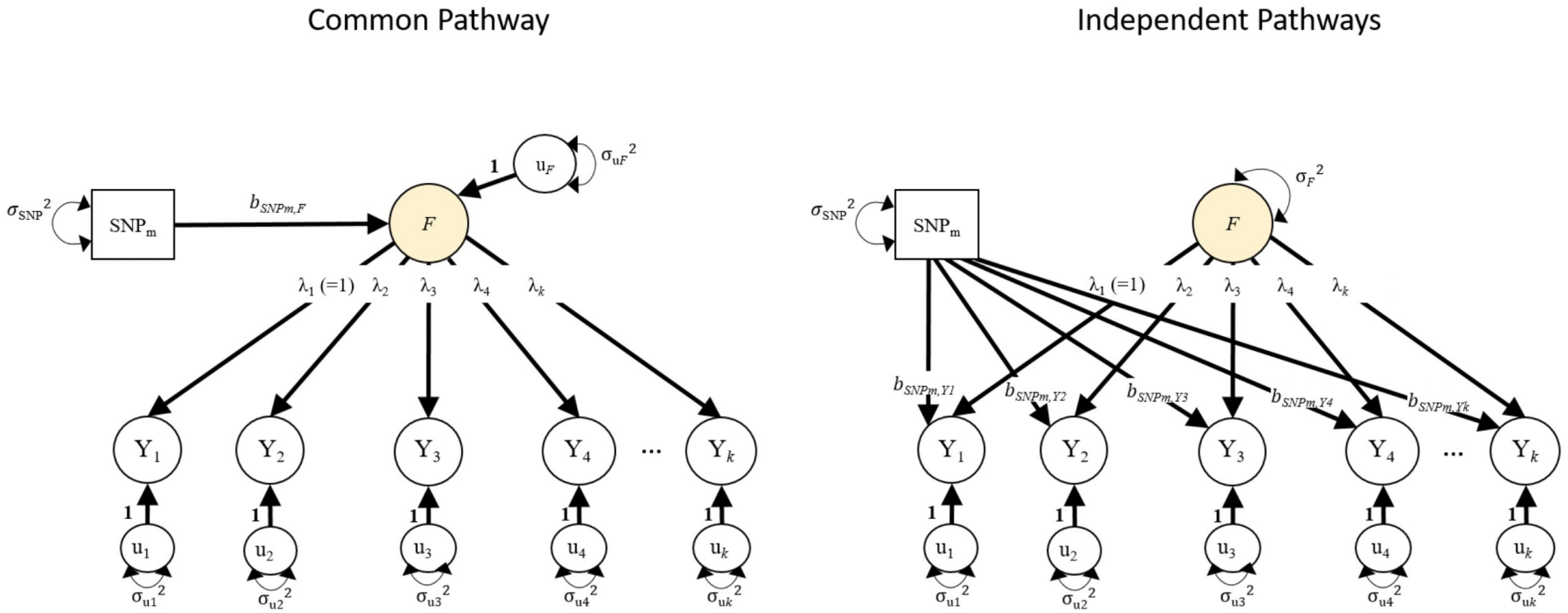
Supplementary Figure 6. Scatterplot of phenotypic and genetic *g* factor loadings. Matrix = Matrix Pattern Completion task; Memory = Memory – Pairs Matching Test; RT = Reaction Time; Symbol Digit = Symbol Digit Substitution Task; TMT-B = Trail Making Test – B; Tower = Tower Rearranging Task; VNR = Verbal Numerical Reasoning Test. Note: the regression intercept of the regression line displayed in this figure is .269, and the unstandardized slope is .970. The intercept of .269 indicates somewhat higher genetic than phenotypic factor loadings, and the slope of .970 indicates close correspondence between their orderings.



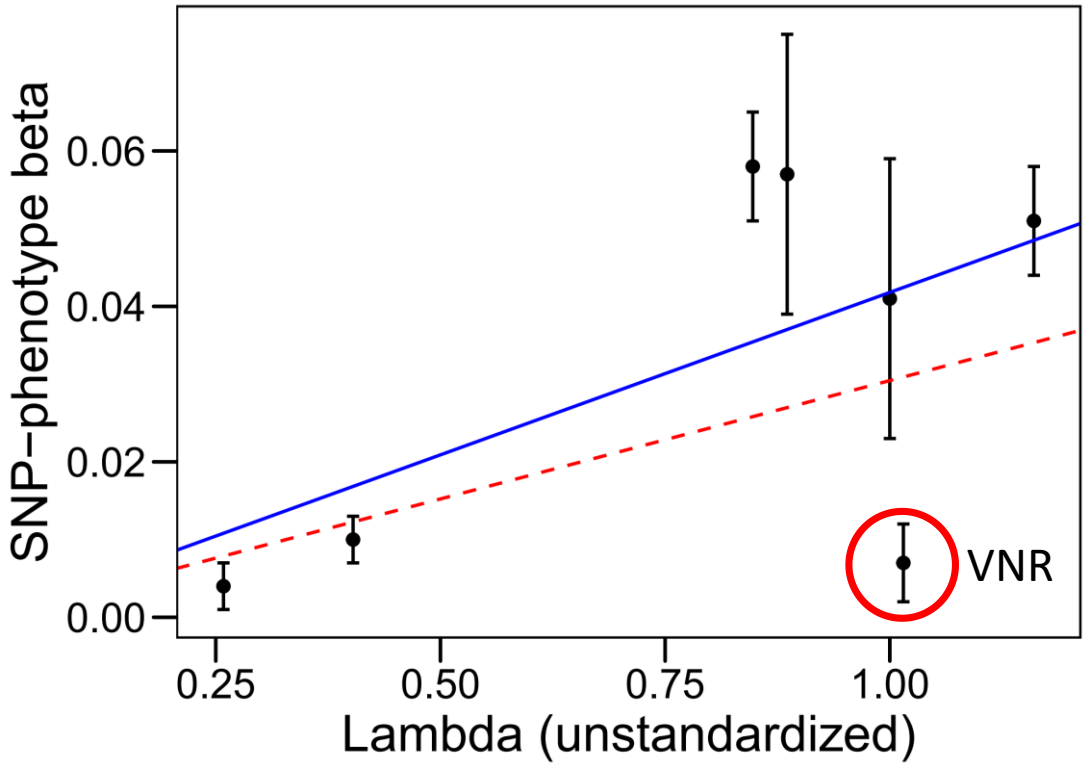
Supplementary Figure 7. Heat-map of LDSC-estimated (observed) and genetic *g* model-implied genetic correlations among UK Biobank cognitive phenotypes. Matrix = Matrix Pattern Completion task; Memory = Memory – Pairs Matching Test; RT = Reaction Time; Symbol Digit = Symbol Digit Substitution Task; Trails-B = Trail Making Test – B; Tower = Tower Rearranging Task; VNR = Verbal Numerical Reasoning Test.



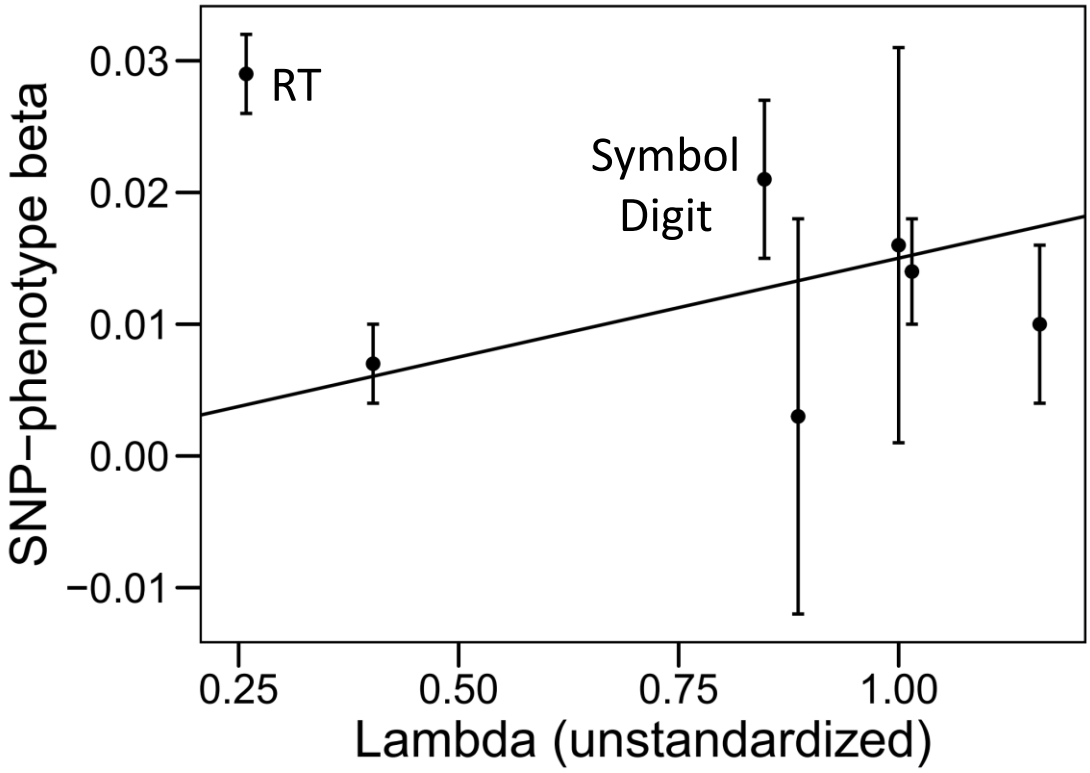
Supplementary Figure 8. Scatterplot of observed and model-implied genetic correlations (from Fig. S7) among UK Biobank cognitive phenotypes. Note: Shaded area represents 95% confidence interval.



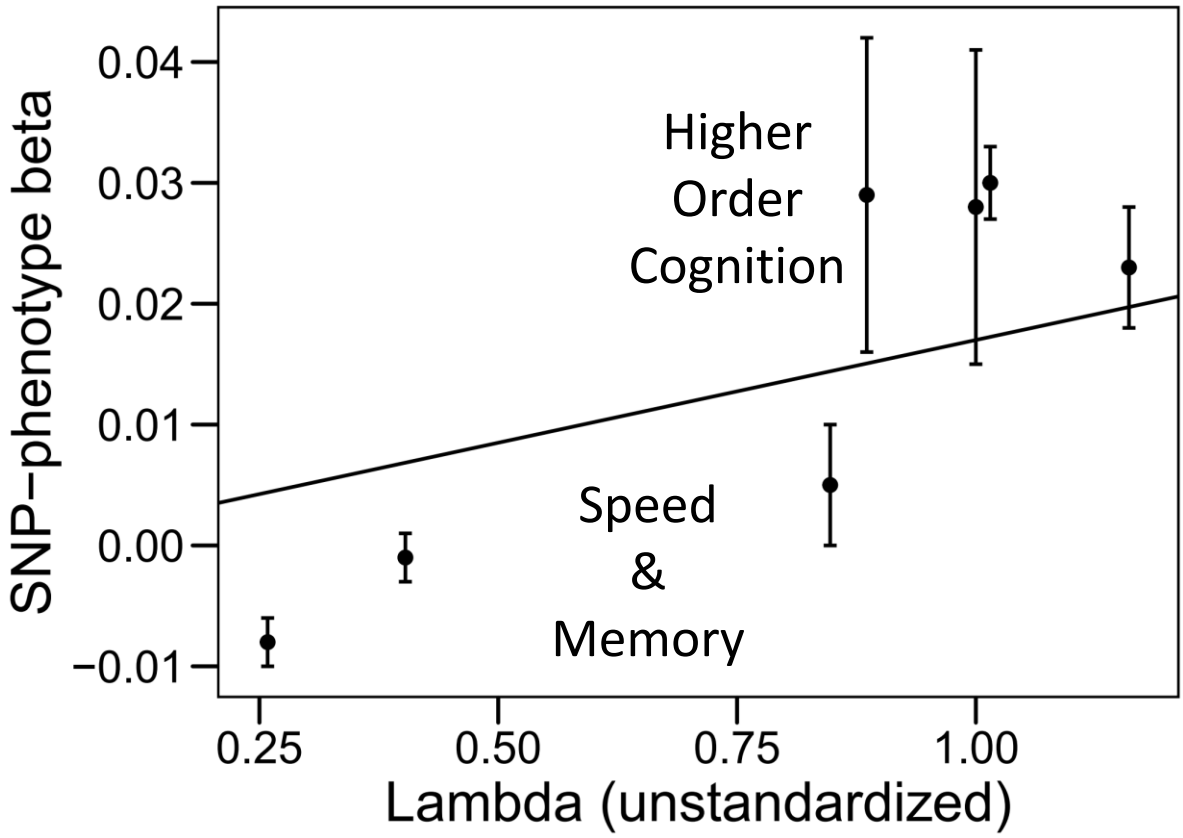
Supplementary Figure 9. Unstandardized path diagrams for *common pathway* (left) and *independent pathways* (right) models used to compute the Genomic SEM heterogeneity statistic (Q) for a multivariate GWAS of a single common factor. In this example, F is a common genetic factor of the genetic components of *k* GWAS phenotypes (Y_1-Y_k). Each model is run once for each SNP, *m.* Single-headed arrows are regression relations, and double-headed arrows are variances. Paths labeled 1 are fixed to 1 for model identification purposes. All other paths represent freely estimated model parameters. Q represents the decrement in model fit of the *common pathway* model relative to the more restrictive *independent pathways* model. Q is a χ^2 distributed test statistic with k-1 degrees of freedom, representing the difference between the *k* SNP-phenotype *b* coefficients in the independent pathways model and the 1 SNP-factor *b* coefficient in the *common pathway* model.



Supplementary Figure 10. Scatter plot of SNP-phenotype regression coefficients (betas) against unstandardized genetic factor loadings for the associated phenotypes, for lead SNP **rs429358** within the APOE gene. Error bars represent standard errors of the SNP-phenotype betas. The dashed red line represents the regression line based on all seven data points. The solid blue line represents the regression line after excluding VNR. In order to correspond directly with Equation S1, both regression lines were estimated with their intercepts fixed to zero, using weights equal to the inverse of the squared standard errors of the betas.



Supplementary Figure 11. Scatter plot of SNP-phenotype regression coefficients against unstandardized genetic factor loadings for the associated phenotypes, for **rs273534** within a locus on Chromosome 17. Error bars represent standard errors of the SNP-phenotype betas. The solid black line represents the regression line based on all seven data points. In order to correspond directly with Equation S1, the regression line was estimated with its intercept fixed to zero, using weights equal to the inverse of the squared standard errors of the betas.



Supplementary Figure 12. Scatter plot of SNP-phenotype regression coefficients against unstandardized genetic factor loadings for the associated phenotypes, for lead SNP **rs2352974** within a locus on Chromosome 3. Error bars represent standard errors of the SNP-phenotype betas. The solid black line represents the regression line based on all seven data points. In order to correspond directly with Equation S1, the regression line was estimated with its intercept fixed to zero, using weights equal to the inverse of the squared standard errors of the betas.

Supplementary Table 1. Phenotypic correlations across UK Biobank's cognitive phenotypes.

	Matrix	Memory	RT	Symbol Digit	Trails-B	Tower	VNR
Matrix	1						
Memory	0.149 (0.009)	1					
RT	0.100 (0.009)	0.074 (0.002)	1				
Symbol Digit	0.300 (0.008)	0.149 (0.003)	0.157 (0.003)	1			
Trails-B	0.339 (0.008)	0.169 (0.003)	0.161 (0.004)	0.490 (0.003)	1		
Tower	0.303 (0.009)	0.158 (0.009)	0.117 (0.009)	0.298 (0.008)	0.335 (0.008)	1	
VNR	0.337 (0.008)	0.142 (0.002)	0.110 (0.002)	0.300 (0.003)	0.401 (0.003)	0.291 (0.008)	1

Note: Matrix = Matrix Pattern Completion task; Memory = Memory – Pairs Matching Test; RT = Reaction Time; Symbol Digit = Symbol Digit Substitution Task; Trails-B = Trail Making Test – B; Tower = Tower Rearranging Task; VNR = Verbal Numerical Reasoning Test. The off-diagonal elements contain the phenotypic correlations across cognitive phenotypes, with standard errors in parentheses.

Supplementary Table 2. SNP-based heritability (SNP h^2; diagonal), LDSC-estimated genetic variance-covariance matrix (lower triangle) and genetic correlation matrix (upper triangle) across UK Biobank's cognitive phenotypes.

	Matrix	Memory	RT	Symbol Digit	Trails-B	Tower	VNR
Matrix	0.155 (0.040)	0.473 (0.081)	0.135 (0.071)	0.544 (0.095)	0.687 (0.094)	0.633 (0.291)	0.869 (0.069)
Memory	0.037 (0.006)	0.040 (0.002)	0.218 (0.029)	0.595 (0.046)	0.618 (0.047)	0.734 (0.095)	0.429 (0.031)
RT	0.014 (0.008)	0.012 (0.002)	0.074 (0.003)	0.357 (0.035)	0.312 (0.032)	0.222 (0.072)	0.169 (0.024)
Symbol Digit	0.071 (0.012)	0.040 (0.003)	0.032 (0.003)	0.110 (0.008)	0.816 (0.056)	0.665 (0.107)	0.551 (0.034)
Trails-B	0.104 (0.014)	0.048 (0.004)	0.033 (0.003)	0.104 (0.007)	0.149 (0.009)	0.693 (0.104)	0.743 (0.038)
Tower	0.084 (0.029)	0.050 (0.006)	0.020 (0.007)	0.074 (0.012)	0.090 (0.014)	0.114 (0.038)	0.670 (0.080)
VNR	0.157 (0.013)	0.040 (0.003)	0.021 (0.003)	0.084 (0.005)	0.132 (0.007)	0.104 (0.012)	0.212 (0.008)

Matrix = Matrix Pattern Completion task; Memory = Memory – Pairs Matching Test; RT = Reaction Time; Symbol Digit = Symbol Digit Substitution Task; Trails-B = Trail Making Test – B; Tower = Tower Rearranging Task; VNR = Verbal Numerical Reasoning Test. The diagonal elements of the matrix contain SNP h^2. The lower off-diagonal elements contain the genetic covariances across cognitive phenotypes, with standard errors in parentheses. The upper off-diagonal elements contain the genetic correlations across cognitive phenotypes, with standard errors in parentheses.

Supplementary Table 3. Intercepts and cross-trait intercepts from LDSC analysis of UK Biobank's cognitive phenotypes.

	Matrix	Memory	RT	Symbol Digit	Trails-B	Tower	VNR
Matrix	1.013						
Memory	0.028	1.002					
RT	0.020	0.086	1.021				
Symbol Digit	0.101	0.077	0.081	1.021			
Trails-B	0.122	0.087	0.079	0.439	1.005		
Tower	0.297	0.027	0.019	0.098	0.118	1.001	
VNR	0.086	0.111	0.096	0.215	0.272	0.074	1.025

Note: Matrix = Matrix Pattern Completion task; Memory = Memory – Pairs Matching Test; RT = Reaction Time; Symbol Digit = Symbol Digit Substitution Task; Trails-B = Trail Making Test – B; Tower = Tower Rearranging Task; VNR = Verbal Numerical Reasoning Test. The diagonal elements of the matrix contain the intercepts from univariate LD score regression (LDSC). Values above 1.0 represent potential population stratification bias in each phenotype. The off-diagonal elements display LDSC cross-trait intercepts, with values over zero representing potential overlap *and* phenotypic correlation for the corresponding pair of phenotypes.

Supplementary Table 4. Unstandardized and standardized common factor solutions for the genetic covariance structure of seven UK Biobank cognitive traits.

		Including Speeded Tests				Excluding Speeded Tests			
		Unstandardized	SE	Standardized	SE	Unstandardized	SE	Standardized	SE
Factor loadings									
	Matrix	0.325	0.028	0.826	0.070	0.393	0.032	1.000	0.082
	Memory	0.131	0.006	0.651	0.031	0.112	0.008	0.555	0.041
	RT	0.084	0.007	0.308	0.026	-	-	-	-
	Symbol Digit	0.275	0.011	0.831	0.034	-	-	-	-
	Trails-B	0.377	0.014	0.976	0.035	-	-	-	-
	Tower	0.288	0.027	0.853	0.080	0.311	0.030	0.921	0.089
	VNR	0.330	0.011	0.717	0.024	0.365	0.023	0.793	0.049
Residual variances									
	Matrix	0.049	0.038	0.317	0.243	0.000	0.039	0.000	0.251
	Memory	0.023	0.002	0.576	0.050	0.028	0.002	0.692	0.061
	RT	0.067	0.003	0.905	0.043	-	-	-	-
	Symbol Digit	0.034	0.006	0.309	0.050	-	-	-	-
	Trails-B	0.007	0.008	0.048	0.051	-	-	-	-
	Tower	0.031	0.034	0.272	0.299	0.017	0.035	0.151	0.310
	VNR	0.103	0.007	0.487	0.033	0.079	0.016	0.371	0.076

Note: Matrix = Matrix Pattern Completion task; Memory = Memory – Pairs Matching Test; RT = Reaction Time; Symbol Digit = Symbol Digit Substitution Task; Trails-B = Trail Making Test – B; Tower = Tower Rearranging Task; VNR = Verbal Numerical Reasoning Test. Standardized factor loadings indicate the lineal relationship between the genetic *g* factor and each of the cognitive phenotypes, ranging from -1 to 1, with 0 representing no relationship. SE = Standard Error. R^2 = percentage of genetic variance of each phenotype accounted for the genetic *g* factor. Residual variances reflect genetic variation unique to each cognitive phenotype. Note: In the model that excluded speeded tests, there was a Heywood case for the Matrix loading. Its residual variance was subsequently constrained to be greater than 0.

Supplementary Table 5. Phenotypic *g* factor CFA estimates for UK Biobank's cognitive phenotypes.

	Including Speeded tests				Excluding Speeded Tests			
	Unstandardized Factor Loadings		Standardized Factor Loadings		Unstandardized Factor Loadings		Standardized Factor Loadings	
Cognitive Phenotype	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Matrix	1.013	0.022	0.501	0.009	1.181	0.028	0.587	0.012
Memory	0.164	0.002	0.257	0.003	0.164	0.004	0.257	0.006
RT	0.040	0.001	0.231	0.003	-	-	-	-
Symbol Digit	2.879	0.019	0.628	0.004	-	-	-	-
Trails-B	0.209	0.001	0.766	0.003	-	-	-	-
Tower	1.522	0.033	0.487	0.009	1.598	0.041	0.514	0.012
VNR	1.055	0.007	0.514	0.003	1.138	0.023	0.555	0.011

Note: Fit indices ($\chi^2(14) = 740.748$, $p < 0.001$; AIC = 1,740,011.718; CFI = 0.985; Tucker-Lewis Index (TLI) = 0.977; Root Mean Square Error of Approximation (RMSEA) = 0.013; SRMR = 0.024) indicated that this model closely approximated the observed phenotypic covariance matrix. Matrix = Matrix Pattern Completion task; Memory = Memory – Pairs Matching Test; RT = Reaction Time; Symbol Digit = Symbol Digit Substitution Task; Trails-B = Trail Making Test – B; Tower = Tower Rearranging Task; VNR = Verbal Numerical Reasoning Test. Standardized factor loadings indicate the linear relationship between the phenotypic *g* factor and each of the cognitive phenotypes, ranging from -1 to 1, with 0 representing no relationship. SE = Standard Error. Z-value = Z statistic value. Residual variances reflect genetic variation unique to each cognitive phenotype. The Reaction Time and Memory tasks were log-transformed to normalize their univariate distributions.

Supplementary Table 6. Genetic correlations of genetic *g* derived from the UK Biobank and genetic results from other major intelligence studies with educational attainment, neural phenotypes, and longevity.

	Genetic g (speeded tests included): Present Study		Genetic g (excluding RT only) Present Study		Genetic g (speeded tests excluded): Present Study		General Cognitive Function: Davies et al. (2018)[12]		Intelligence: Savage et al. (2018)[13]		Intelligence: Hill et al. (2019)[14]	
	r	SE	*r*	SE	*r*	SE	*r*	SE	*r*	SE	*r*	SE
Educational Attainment: (Lee et al., 2018)[15]	0.475	0.021	0.502	0.020	0.554	0.024	0.694	0.013	0.730	0.024	0.847	0.009
Alzheimer's Disease: Lambert et al. (2013)[16]	-0.341	0.057	-0.353	0.059	-0.329	0.070	-0.326	0.058	-0.29	0.077	-0.327	0.055
Autism Spectrum Disorder: Grove et al. (2019)[17]	0.095	0.043	0.092	0.043	0.173	0.043	0.203	0.035	0.234	0.038	0.205	0.033
ADHD: Demontis et al. (2019)[18]	-0.233	0.038	-0.264	0.038	-0.323	0.040	-0.376	0.034	-0.379	0.041	-0.462	0.033
Schizophrenia: Lee et al. (2019)[19]	-0.375	0.027	-0.348	0.027	-0.321	0.032	-0.235	0.022	-0.206	0.026	-0.134	0.021
Total Brain Volume: Zhao et al. (2019)[20]	0.195	0.040	0.201	0.040	0.253	0.044	0.229	0.037	0.229	0.051	0.250	0.037
Longevity: Timmers et al. (2019)[21]	0.255	0.030	0.260	0.029	0.290	0.031	0.320	0.027	0.284	0.036	0.377	0.025

Note: All correlations are statistically significant at $p < 0.001$, except r Genetic g with ASD ($p = 0.029$). ADHD = Attention Deficit Hyperactivity Disorder. *r* = Pearson correlation coefficient. SE = Standard Error.

Supplementary References

1. Gelman, A. & Stern, H. The difference between 'significant' and 'not significant' is not itself statistically significant. *Am. Stat.* (2006) doi:10.1198/000313006X152649.
2. Deary, I. J. Intelligence. *Curr. Biol.* **23**, R673–R676 (2013).
3. Carroll, J. B. The Identification and Description of Cognitive Abilities. in *Human Cognitive Abilities: A Survey of Factor-Analytic Studies* (Cambridge University Press, 1993). doi:10.1017/CBO9780511486371.
4. Tucker-Drob, E. M. Differentiation of Cognitive Abilities Across the Life Span. *Dev. Psychol.* **45**, 1097–1118 (2009).
5. Spearman, C. 'General Intelligence,' Objectively Determined and Measured. *Am. J. Psychol.* (1904) doi:10.2307/1412107.
6. Spearman, C. *The abilities of man*. (Macmillan Oxford, 1927).
7. Thurstone, L. L. *Primary Mental Abilities*. (The University of Chicago Press, 1938).
8. Burt, C. *The Factors of the Mind*. (University of London Press, 1940).
9. Vernon, P. E. *The Measurement of Abilities*. (University of London Press, 1940).
10. Horn, J. L. & Cattell, R. B. Age differences in fluid and crystallized intelligence. *Acta Psychol. (Amst).* (1967) doi:10.1016/0001-6918(67)90011-x.
11. Johnson, W., Nijenhuis, J. te & Bouchard, T. J. Still just 1 g: Consistent results from five test batteries. *Intelligence* (2008) doi:10.1016/j.intell.2007.06.001.
12. Davies, G. *et al.* Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. *Nat. Commun.* (2018) doi:10.1038/s41467-018-04362-x.
13. Savage, J. E. *et al.* Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat. Genet.* (2018) doi:10.1038/s41588-018-0152-6.
14. Hill, W. D. *et al.* A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence. *Mol. Psychiatry* (2019) doi:10.1038/s41380-017-0001-5.
15. Kovas, Y. & Plomin, R. Generalist genes: implications for the cognitive sciences. *Trends Cogn. Sci.* (2006) doi:10.1016/j.tics.2006.03.001.
16. Lambert, J. C. *et al.* Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat. Genet.* (2013) doi:10.1038/ng.2802.
17. Grove, J. *et al.* Identification of common genetic risk variants for autism spectrum disorder. *Nat. Genet.* (2019) doi:10.1038/s41588-019-0344-8.
18. Demontis, D. *et al.* Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat. Genet.* (2019) doi:10.1038/s41588-018-0269-7.
19. Lee, P. H. *et al.* Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell* (2019) doi:10.1016/j.cell.2019.11.020.

20. Zhao, B. *et al.* Large-scale GWAS reveals genetic architecture of brain white matter microstructure and genetic overlap with cognitive and mental health traits (n = 17,706). *Mol. Psychiatry* (2019) doi:10.1038/s41380-019-0569-z.

21. Timmers, P. R. *et al.* Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances. *Elife* (2019) doi:10.7554/eLife.39856.