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A general dimension of genetic sharing across diverse cognitive traits inferred from molecular data

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It has been known since 1904 that, in humans, diverse cognitive traits are positively intercorrelated. This forms the basis for the general factor of intelligence (*g*). Here, we directly test whether there is a partial genetic basis for individual differences in *g* using data from seven different cognitive tests ($n = 11{,}263$–$331{,}679$) and genome-wide autosomal single-nucleotide polymorphisms. A genetic *g* factor accounts for an average of 58.4% (s.e. = 4.8%) of the genetic variance in the cognitive traits considered, with the proportion varying widely across traits (range, 9–95%). We distil genetic loci that are broadly relevant for many cognitive traits (*g*) from loci associated specifically with individual cognitive traits. These results contribute to elucidating the aetiology of a long-known yet poorly understood phenomenon, revealing a fundamental dimension of genetic sharing across diverse cognitive traits.

Scores on psychometric tests of cognitive abilities are prospectively associated with educational performance, socio-economic attainments, everyday functioning, health and longevity[1–3]. In 1904, Charles Spearman identified a positive manifold of intercorrelations among school test results and estimates of intelligence, leading him to propose that they arise from a single general dimension of variation, which he termed general intelligence (and which he denoted as *g*)[4]. He theorized that most of the remaining variance in each cognitive test was accounted for by a factor specific to that test, which he called *s*. Thus, some variance in each cognitive test was thought to be shared with all other cognitive tests (*g*), and some was thought to be specific to that test (its *s*). Hundreds of studies have since replicated the finding that, when many diverse cognitive tests are administered to a sizeable sample of people, a *g* factor is found that accounts for between about 25% and 50% of the total test variance, depending on the specific composition of the participants and test battery[5–7]. Considerable efforts over the past century have been placed on identifying biological associations with *g*, spanning levels of analysis from molecular, to neuro-anatomical, to cognitive[8–12].

Psychometrically, a hierarchical structure of cognitive abilities is commonly agreed, with cognitive tests' variance accounted for by three different strata of variation (Supplementary Fig. 1), representing (1) each test's specific variance (*s*), (2) broad domains of cognitive function (for example, reasoning, processing speed, memory) and (3) *g* (ref. [5]). All cognitive tests have some *g* loading, though this varies from test to test. Twin studies that have employed multivariate methods to examine genetic associations within the hierarchy of cognitive test score variance[13] indicate a strong heritable basis for *g*, suggesting that cognitive traits are positively correlated substantially because of strongly overlapping genetic architecture[14–18]. Multivariate approaches, however, have not yet been combined with the modern molecular genetic methods needed to separate general from specific genetic associations with cognitive traits at the level of individual genetic loci.

Genome-wide association studies (GWAS) have been applied to individual cognitive measures or composite scores formed from multiple such cognitive measures[19–23]. However, existing univariate approaches are limited in their capability in separating *g* from *s* variance. In the case of GWAS of individual cognitive tests—for example, a measure of verbal declarative memory or processing speed—the identified loci could be related to *g* and/or to the named cognitive property[22,23]. This is a common limitation in both phenotypic and genetic cognitive studies[24]. Here we sought to test for a genetic *g* factor directly, using genomic structural equation modelling (Genomic SEM[25]), a multivariate, genome-wide molecular genetics approach. We model both shared and unique genome-wide architecture in aggregate across the entirety of the genome, and we distinguish individual variants that are broadly relevant for many cognitive traits (via genetic *g*) from those associated with only individual cognitive traits (via genetic *s* factors). Thus, this investigation attempts to provide insights into the shared genetic architecture across multiple cognitive traits and affords the explicit identification of genetic variants underlying *g*.

Results

Data for the present study came from the UK Biobank (UKB), a biomedical cohort study that collects a wide range of genetic and health-related measures from a population-based sample of community-dwelling participants in the United Kingdom. Participants were measured on up to seven cognitive traits using tests that often show substantial concurrent validity with established psychometric tests of cognitive abilities, and modest to good test–retest reliability[26]: reaction time (RT, $n = 330{,}024$, which assesses perceptual

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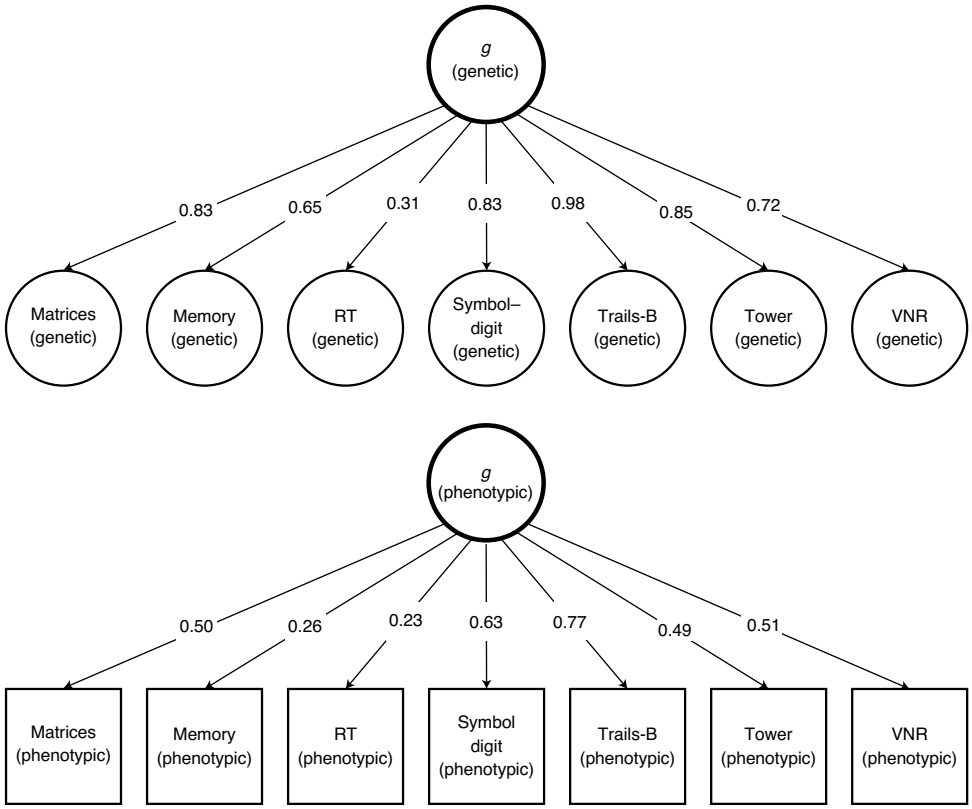

Fig. 1 | Standardized genetic and phenotypic factor solutions for the covariance structure of seven UKB cognitive traits used in the present study. Squares represent observed variables (the phenotypes that are directly measured). Circles represent latent variables that are statistically inferred from the data—that is, the genetic (top) and phenotypic (bottom) *g* factors that are inferred through factor analysis and the genetic components of the observed phenotypes that are inferred through LDSC. Arrows are standardized factor loadings, which can be interpreted as standardized regression relations with the arrow pointing from the predictor variable to the outcome variable. Genetic factor models were estimated using Genomic SEM, and phenotypic models were estimated using the lavaan package for R. Matrix, matrix pattern completion task; memory, memory pairs-matching test; symbol digit, symbol digit substitution task; tower, tower rearranging task. All variables are scaled such that higher scores indicate better cognitive performance. The genetic *g* factor accounts for an average of 58.37% of genetic variance in the seven cognitive traits. The phenotypic *g* factor accounts for an average of 26.50% of observed phenotypic variance in the seven cognitive traits.

motor speed); matrix pattern recognition ($n = 11{,}356$, non-verbal reasoning); verbal numerical reasoning (VNR, $n = 171{,}304$, verbal and numeric problem solving; the test is called 'fluid intelligence' in UKB); symbol digit substitution ($n = 87{,}741$, information processing speed); memory pairs-matching test ($n = 331{,}679$, episodic memory); tower rearranging ($n = 11{,}263$, executive functioning); and trail-making test-B (trails-B, $n = 78{,}547$, executive functioning). Scores on all tests were coded such that higher scores represented more optimal (that is, faster or more accurate) performance.

Phenotypic covariance structure. A positive manifold of phenotypic correlations was observed across the seven cognitive traits. All correlations were positive, ranging from 0.074 to 0.490, indicating that more optimal performance on a given test is associated with more optimal performance on the other tests (Supplementary Fig. 1 and Supplementary Table 1). The mean phenotypic correlation was 0.232. In principal component analysis (PCA), the first unrotated component accounted for a total of 35.8% of the phenotypic variance. A confirmatory factor model with a single common *g* factor (Fig. 1, bottom) fit the phenotypic covariance matrix well ($\chi^2(14) = 740.748$, $P < 0.001$; standardized root mean square residual (SRMR) = 0.024; comparative fit index (CFI) = 0.985; root mean square error of approximation (RMSEA) = 0.013). Table 1 reports both the proportion of phenotypic *g*/phenotypic *s* variance for each cognitive trait, and the respective absolute contributions. The *g* factor accounted for 26.5% (s.e. = 0.2%) of variance in the seven cognitive traits. That this proportion is appreciably lower than that obtained from the PCA highlights the distinction between factor analysis, which formally models the effects of factors on constellations of variables, and PCA, which simply seeks to maximize the variance of a weighted linear composite of those variables. All of the standardized loadings were statistically significant, ranging from 0.231 to 0.766 ($M = 0.48$, s.d. = 0.19).

Multivariate genome-wide architecture. We next aimed to estimate the extent of genetic sharing across the cognitive traits using molecular genetic data. We used a multivariable version of linkage disequilibrium score regression (LDSC)[27] implemented in Genomic SEM[25] to estimate genetic correlations among the cognitive traits. Prior to this formal modelling, we conducted descriptive analyses of the cognitive traits' genetic correlations, similar to those often conducted on cognitive phenotypes. We report those descriptive analyses' results first.

As was first reported at the phenotypic level by Spearman in 1904 (ref. [4]), we identified, using LDSC, a positive manifold of genetic correlations among the UKB cognitive traits, ranging from 0.135 to 0.869 ($M = 0.53$, s.d. = 0.22; Supplementary Fig. 3 and Supplementary Tables 2 and 3). The mean genetic correlation was 0.530, and the first principal component accounted for a total of 62.17% of the genetic variance. Using genomic-relatedness-based

Table 1 | Common factor solutions for the genetic (top) and phenotypic (bottom) covariance structure of seven UKB cognitive traits

	Standardized factor loadings		Common (*g*) and specific (*s*) sources of genetic variation				
	Genetic *g*		Proportion of genetic variation explained by genetic *g* and genetic *s*		Proportion of phenotypic variation explained by genetic *g* and genetic *s* (HapMap3 common variants only)		
Cognitive trait	**Estimate**	**s.e.**	**Common (*g*), %**	**Specific (*s*), %**	**Common (*g*), %**	**Specific (*s*), %**	**Total SNP h^2**
Matrices	0.826	0.070	68.23	31.77	10.60	4.90	15.50
Memory	0.651	0.031	42.38	57.62	1.70	2.30	4.00
RT	0.308	0.026	9.49	90.51	0.70	6.70	7.40
Symbol digit	0.831	0.034	69.06	30.94	7.60	3.40	11.00
Trails-B	0.976	0.035	95.26	4.74	14.20	0.70	14.90
Tower	0.853	0.080	72.76	27.24	8.30	3.10	11.40
VNR	0.717	0.024	51.41	48.59	10.90	10.30	21.20
Mean (%)			58.36	41.64	7.71	4.49	12.20
	Phenotypic *g*		**Proportion of phenotypic variation explained by phenotypic *g* and phenotypic *s***				
Cognitive trait	**Estimate**	**s.e.**	**Common (*g*), %**	**Specific (*s*), %**			
Matrices	0.501	0.009	25.10	74.90			
Memory	0.257	0.003	6.60	93.40			
RT	0.231	0.003	5.34	94.66			
Symbol digit	0.628	0.004	39.44	60.56			
Trails-B	0.766	0.003	58.68	41.32			
Tower	0.487	0.009	23.72	76.28			
VNR	0.514	0.003	26.42	73.58			
Mean (%)			26.50	73.50			

All traits are scaled such that higher scores indicate higher cognitive performance. Total single-nucleotide polymorphism (SNP) h^2 = total proportion of phenotypic variance in the corresponding cognitive trait accounted for by all tagged common variants. By definition, the common (*g*) and specific (*s*) proportional contributions to total phenotypic variation sum to total SNP h^2, and the common (*g*) and specific (*s*) proportional contributions to genetic variation sum to 100%. Standardized factor loadings indicate the standardized linear relationship between the factor and each of the cognitive outcomes. Models are fit to LDSC-derived genetic covariance matrices using Genomic SEM. As per best practices for LDSC, genetic covariance matrices were derived using HapMap3 SNPs with minor allele frequencies >1%, excluding SNPs with imputation quality (INFO) < 0.9 and those from the major histocompatibility complex (MHC) region.

restricted maximum likelihood (GCTA–GREML)[28,29], a different estimator of the genetic correlations among the seven cognitive traits (Supplementary Fig. 4), the mean genetic correlation was 0.502, and the first principal component accounted for 61.24% of the genetic variance. The correlation between LDSC- and GCTA–GREML-derived genetic correlations was $r = 0.947$, indicating very close correspondence between the results of the two methods (Supplementary Fig. 5).

We then proceeded with Genomic SEM to formally model the genetic covariance matrix. This allowed us to evaluate the fit of the genetic *g* factor model, estimate s.e. for model parameters, estimate genetic correlations with collateral phenotypes and incorporate genetic *g* explicitly into multivariate discovery. We applied Genomic SEM to fit a single common factor model to the LDSC-derived genetic covariance matrix among the seven cognitive traits. This model specified the genetic component of each cognitive trait to load on a single common factor, which we term genetic *g*. For each trait, we additionally estimated residual, trait-specific genetic variance components (genetic *s*). Thus, we formally distil the molecular genetic contributions of *g* and *s* to heritable variation in each of the cognitive traits, and test the fit of this model. Fit indices ($\chi^2(14) = 117.019$, $P < 0.001$; CFI = 0.970; SRMR = 0.088) indicated that the factor model closely approximated the observed genetic covariance matrix (Supplementary Figs. 7 and 8). Figure 1 displays the standardized estimates for this model (top) and the standardized estimates from a phenotypic factor model (bottom) fitted to the phenotypic covariance matrix (Supplementary Fig. 5 and Supplementary Table 1). A factor model that constrained the standardized genetic factor loadings to be equal to the standardized point estimates for loadings from the phenotypic model produced a substantial decrement in model fit ($\chi^2(7) = 823.037$, $P < 0.001$), indicating that the genetic and phenotypic factor structures were not strictly equivalent. Indeed, the standardized genetic factor loadings were consistently higher in magnitude than the standardized phenotypic factor loadings, but there was a strong linear association between them (Supplementary Fig. 6). Table 1 reports the proportions of genetic *g* and genetic *s* variance for each cognitive trait, and the respective absolute contributions. The genetic *g* factor accounted for 58.36% (s.e. = 4.84%) of the genetic variance in the seven cognitive traits. All of the standardized loadings on genetic *g* were statistically significant, ranging from 0.308 to 0.976 ($M = 0.74$, s.d. = 0.22).

The proportion of genetic variation in each trait accounted for by genetic *g* differed substantially across traits. Supporting this inference, a factor model that constrained the standardized genetic factor loadings to be equal across traits produced a substantial decrement in model fit ($\chi^2(12) = 749.122$, $P < 0.001$). Four of the cognitive traits have a genetic contribution to their variance that is derived principally from genetic *g* and much less from genetic *s*; these are trails-B (95.26% genetic *g*; 4.74% genetic *s*), tower (72.76% genetic *g*; 27.20% genetic *s*), symbol digit (69.06% genetic *g*; 30.94% genetic *s*) and matrices (68.23% genetic *g*; 31.77% genetic *s*). VNR

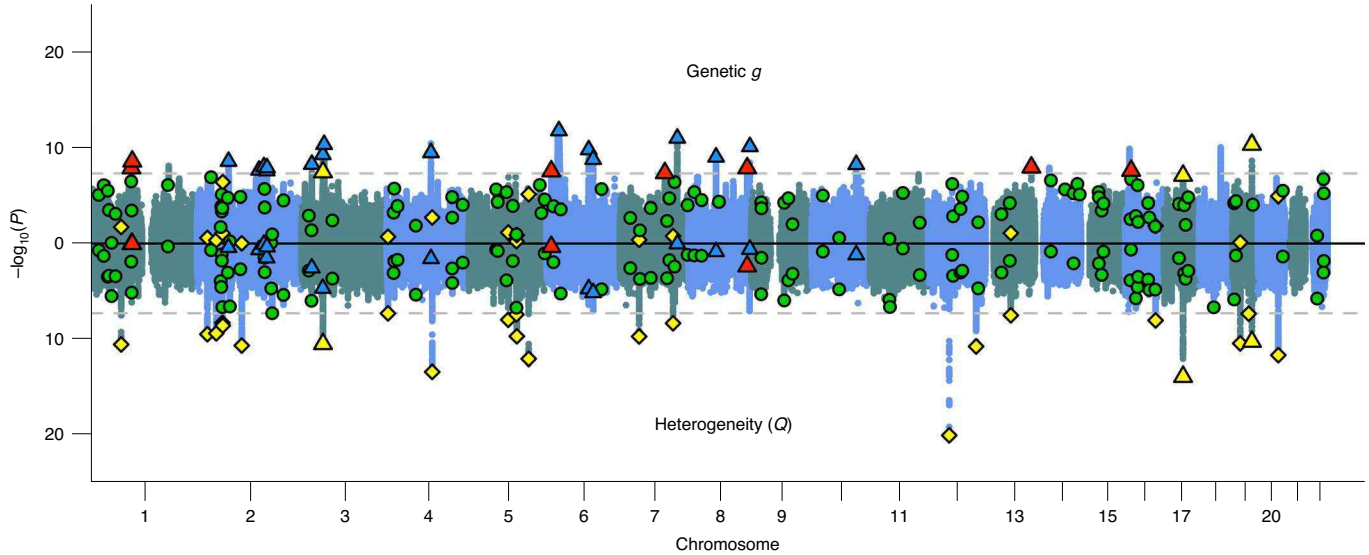

Fig. 2 | Miami plot of unique, independent hits for genetic *g* and *Q* (7,857,346 variants). The heterogeneity statistic (*Q*) indexes whether a SNP evinces patterns of association with cognitive traits departing from the pattern that would be expected if it were to act on the traits via genetic *g*. Thus, genetic *g* loci in common with *Q* loci are false discoveries on genetic *g*. The dashed grey horizontal lines denote the genome-wide significance threshold ($P < 5 \times 10^{-8}$). The genome-wide significant loci represented by the triangles, circles and diamonds are shown in both upper and lower parts of the Miami plot, with their locations corresponding to the $-\log_{10}(P)$ of their associations with genetic *g* (upper) and the $-\log_{10}(P)$ of their *Q* statistic (lower). Red triangles, genetic *g* loci unique to univariate loci; blue triangles, genetic *g* loci in common with univariate loci; green circles, univariate loci unique to genetic *g* loci; yellow triangles, genetic *g* loci in common with *Q* loci; yellow diamonds, *Q* loci unique to genetic *g* loci.

(51.41% genetic *g*; 48.59% genetic *s*) and memory (42.38% genetic *g*; 57.62% genetic *s*) are more evenly split. RT has the majority of its genetic influence from genetic *s* (9.49% genetic *g*, 90.51% genetic *s*). We emphasize one important implication of these results, which is that univariate genetic analyses (for example, GWAS) of some of these individual traits will largely reveal results relevant to *g* rather than to the specific abilities thought to be required to perform the test[24]. As the prespecified model was parsimonious and the fit was close, we chose to forego implementing data-driven exploratory steps to further improve fit. Supplementary Tables 4 and 5 report full parameter estimates for genetic and phenotypic factor models.

Multivariate genome-wide discovery. We next aimed to determine the contributions of individual genetic loci specifically to genetic *g*, and to distil those from loci associated with other levels of the cognitive hierarchy. We fit a multivariate GWAS of genetic *g* within Genomic SEM[25] to distinguish loci relevant to genetic *g* from loci whose patterns of association across the individual traits are inconsistent with their operation on genetic *g*, as indexed by the heterogeneity statistic, *Q*. We provide detailed explication of the *Q* statistic and how it can be appropriately interpreted in the section 'Interpreting the heterogeneity statistic' in Supplementary Information.

The GWAS results for genetic *g* and *Q* are displayed in Fig. 2 as a Miami plot, with further information provided in Table 2. Our method distinguishes four types of genome-wide significant loci. First, highlighted in red are genome-wide significant loci for genetic *g* that are not genome-wide significant loci for the univariate GWAS analyses of individual traits. These are loci influencing general intelligence identified by leveraging the joint genetic architecture of the traits. Second, highlighted in blue are genome-wide significant loci for *g* that are also genome-wide significant loci in the univariate GWAS analyses for at least one individual cognitive trait. These loci might otherwise have been interpreted as relevant specifically to the individual trait, when in fact the multivariate results indicate that they are relevant to genetic *g*[24]. Third, highlighted in green are genome-wide significant loci for univariate phenotypes that are not genome-wide significant loci for *g*. These might be loci that are specific to the individual traits, but not genetic *g*. Fourth, highlighted in yellow are loci that evince genome-wide significant heterogeneity (*Q*), indicating that they show patterns of associations with cognitive traits departing from the pattern that would be expected if they were to act on the traits via genetic *g*. *Q* findings that exceed the genome-wide significance threshold for genetic *g* (yellow triangles) are implicated as false discoveries on genetic *g* that are likely driven by a strong signal in a subset of cognitive traits or in a single cognitive trait. The *Q* statistic helps to safeguard against these false discoveries. The *Q* findings that do not surpass the genome-wide significance threshold for genetic *g* (yellow diamonds) are not significantly related to genetic *g* but are significantly heterogeneous in their patterns of association with the cognitive traits. These loci may be relevant to specific cognitive traits, or to cognitive domains that are intermediate in specificity and generality between *g* and *s*, but not to general intelligence (see Supplementary Fig. 1). Note that these four types of genome-wide significant loci are represented in both the top and bottom panels of the Miami plot, with their locations corresponding to the $-\log_{10}(P)$ of their associations with genetic *g* in the top panel, and with the $-\log_{10}(P)$ of their *Q* statistic in the bottom panel.

Overall we identified 30 genome-wide significant ($P < 5 \times 10^{-8}$) loci associated with genetic *g*. Of these, 18 (60%) have previously been reported as hits for cognitive tests (five loci) and/or cognitively relevant phenotypes, such as educational attainment or highest maths course taken (16 loci) in GWAS that did not include data from UKB. Of the 18 genetic *g* hits that replicated outside of UKB, 16 were also hits on at least one cognitive test included in the multivariate UKB analysis. Of the 30 total genetic *g* loci, 12 were discoveries specific to UKB, five of which were specific to the present study's multivariate modelling and seven of which were also hits on at least one cognitive test included in the multivariate UKB analysis. Thus, of the 30 total loci that were found here to be associated with genetic *g*, 23 were in common with the univariate GWAS of

Table 2 | Summary of multivariate (genetic *g*) and univariate GWAS results

Outcome	Significant loci ($P<5\times10^{-8}$)	Independent of univariate loci	Independent of *Q* loci	Common with loci previously reported for cognitive tests and cognitively relevant traits[a] in GWAS that did not include UKB	Mean $\chi^2(1)$	LDSC intercept	λ_{GC}
Multivariate GWAS							
Genetic *g*	30	7	27	18	1.471	0.973	1.373
	Significant loci ($P<5\times10^{-8}$)	**Independent of univariate loci**	**Independent of genetic *g* loci**	**Common with loci previously reported for cognitive tests and cognitively relevant traits[a] in GWAS that did not include UKB**	**Mean $\chi^2(1)$**		
Heterogeneity (*Q*)	24	9	21	5	1.337		
Univariate GWAS							
	Significant loci ($P<5\times10^{-8}$)	**Independent of genetic *g* loci**	**Independent of *Q* loci**		**Mean χ^2**		
Matrices ($n=11,356$)	0	-	-		1.040	1.013	1.033
Memory $n=331,679$)	10	9	7		1.223	1.002	1.187
RT ($n=330,024$)	39	34	23		1.420	1.021	1.318
Symbol digit ($n=87,741$)	1	0	0		1.188	1.021	1.169
Trails-B ($n=78,547$)	7	1	5		1.203	1.005	1.177
Tower ($n=11,263$)	0	-	-		1.022	1.001	1.025
VNR ($n=171,304$)	89	71	83		1.640	1.025	1.471

The same 7,857,346 variants were used for univariate and multivariate GWAS. Genome-wide significant loci that were 250 kb or closer were merged into a single locus. Here we report loci that are independent from each other at $r^2<0.1$. $^{\lambda}$GC, genomic inflation factor. For *Q*, mean χ^2 was calculated by conversion of *Q* statistics (which are χ^2 distributed with six degrees of freedom) to distributed test statistics with one degree of freedom, and then taking their mean. Matrices, matrix pattern completion task; memory, memory pairs-matching test; symbol digit, symbol digit substitution task; tower, tower rearranging task. Supplementary Tables 8–28 report the individual SNPs, loci and, for those reported in previous studies, the references for the studies and implicated phenotypes. [a]Cognitive tests and cognitively relevant traits include performance-based cognitive test scores, educational attainment, self-reported maths ability and highest maths course taken.

individual cognitive traits that served as the basis for our multivariate analysis, indicating that seven loci were discoveries specific to multivariate modelling (Supplementary Tables 15 and 22). An LDSC analysis of genetic *g* GWAS summary statistics yielded an intercept slightly <1.0, indicating that inflation of the test statistics (mean $\chi^2(1)=1.471$; $\lambda_{GC}=1.373$) was attributable to true polygenic signal rather than to under-controlled population stratification.

We identified a total of 24 genome-wide significant loci for *Q*, three of which were significantly associated with genetic *g* (and therefore likely to be relevant to more specific cognitive traits and false discoveries on *g*) and 15 of which were significantly associated with at least one individual cognitive trait in the test-specific GWAS (and may therefore be interpreted as hits for more specific cognitive traits, rather than for a general dimension of cognitive function). Of the 24 loci for *Q*, five (21%) have previously been reported as hits for cognitive tests (one locus) and/or cognitively relevant phenotypes (four loci) in GWAS that did not include data from UKB, and 19 loci were specific to UKB (Supplementary Tables 16 and 23). Two of the *Q* loci previously reported in non-UKB GWAS were also genetic *g* loci (but, because they were Q hits, are most likely to be false discoveries for genetic *g* and more relevant to specific cognitive traits).

Inspection of univariate GWAS results for the individual traits may help to determine the sources of heterogeneity for the *Q* findings. For instance, a SNP (rs429358) within *APOE*, which is a known risk factor for Alzheimer's disease[30], was a significant *Q* finding. With the exception of its association with VNR, this SNP displayed a pattern of association with traits corresponding closely with the degree to which they represented genetic *g*. However, consistent with the inference that *APOE* is specifically relevant for cognitive ageing, the SNP displayed a negligible null association with VNR ($P=0.142$), which is a test that shows minimal age-related differences in the UKB data[31]. Another example of a *Q* finding is located on chromosome 17 (chr17:44021960–44852612), which was reported to be significantly associated with both general cognitive ability and RT[19]. From the univariate GWAS results, the largest association for this locus was with RT, a measure of psychomotor speed with a relatively low loading on genetic *g*. This locus may have a particularly pronounced association with speeded abilities, rather than a general association with genetic *g*. The third *Q* locus that is also significant for genetic *g* is located on chromosome 3 (chr3:49120040–50234126). This locus has previously reported associations with general cognitive ability, educational attainment, intelligence and maths ability[19–21,32]. In the current study, this locus demonstrates significant heterogeneity and displays its largest associations with VNR, tower, matrices and trails-B, all measures of higher-order cognition. Its associations with measures of speed and episodic memory (arguably more basic cognitive processes) are negligible.

Genetic correlations with external GWAS traits. As expected, the genetic *g* factor identified here displayed strong but imperfect genetic correlations (as estimated by LDSC) with general cognitive function from Davies et al.[19] ($r_g=0.90$, s.e.$=0.02$) and Savage et al.[21] ($r_g=0.87$, s.e.$=0.05$), which were univariate GWAS of broad cognitive phenotypes, and that from Hill et al.[20] ($r_g=0.80$, s.e$=0.02$), which was a GWAS of intelligence that incorporated educational attainment GWAS summary statistics to boost power via multi-trait analysis of GWAS[33]. As reported in Supplementary

Table 6, genetic *g* had a positive genetic correlation with educational attainment[32] ($r_g = 0.48$, s.e. = 0.02) that is lower than those found between education and previous GWAS of cognitive ability (all estimated at $r > 0.69$)[19–21]. To determine whether this lower association was driven by the inclusion of RT, or more generally with speeded measures as indicators of genetic *g*, we re-estimated the genetic correlations using a genetic *g* factor formed from the cognitive traits that excluded either RT or all speeded measures (RT, trails-B and symbol digit). The version of the genetic *g* factor that excluded RT accounted for 66.76% (s.e. = 5.85%) of the genetic variance in the six remaining cognitive traits, and the version that excluded all speeded tests accounted for 69.66% (s.e. = 8.08%) of the genetic variance in the four remaining cognitive traits. These versions of genetic *g* produced somewhat higher genetic correlations between genetic *g* and educational attainment ($r_g = 0.50$ when excluding RT, $r_g = 0.55$ when excluding all three speeded measures) that continued to be lower than those found between educational attainment and previous GWAS of general cognitive ability.

Negative genetic correlations were found between genetic *g* and Alzheimer's disease[34] ($r_g = -0.34$, s.e. = 0.06), schizophrenia[35] ($r_g = -0.38$, s.e. = 0.03) and attention deficit, hyperactivity disorder (ADHD)[36] ($r_g = -0.23$, s.e. = 0.04). Additionally, genetic *g* had significant positive genetic associations with total brain volume[37] ($r_g = 0.20$, s.e. = 0.04) and longevity[38] ($r_g = 0.26$, s.e. = 0.03) (Supplementary Table 6). Notably, the negative genetic association between genetic *g* and schizophrenia was substantially stronger than that obtained for associations between other GWAS of cognitive function and schizophrenia, and contrasts substantially with the mild positive genetic correlation that has been reported between educational attainment and schizophrenia[39]. Genetic associations between genetic *g* and Alzheimer's disease, ASD, ADHD, total brain volume and longevity were similar to those obtained for other GWAS of cognitive function, particularly when the speeded tests were removed from the genetic *g* factor.

Replication of positive genetic manifold and polygenic prediction in Generation Scotland. We sought to confirm key results in the independent Generation Scotland study ($n = 6{,}950$ unrelated individuals). The cognitive measures in Generation Scotland were Wechsler Logical Memory (episodic memory), Mill Hill Vocabulary (crystallized knowledge), Wechsler Digit Symbol Substitution (processing speed) and Verbal Fluency (semantic fluency), as described previously[40,41]. Because the sample size of Generation Scotland is too small to produce stable estimates of heritability and genetic correlation within LDSC, it was not feasible to directly integrate these analyses into the above Genomic SEM models to estimate joint models with the UKB phenotypes and other external GWAS traits. Instead, we estimated a genetic correlation matrix for the four cognitive tests in Generation Scotland using GCTA–GREML[28,29], which is more appropriate than LDSC for moderately sized samples such as this. The average genetic correlation in this matrix was 0.517, and eigen decomposition indicated that the percentage of genetic variance explained by a single principal component was 64.90%. These two values are similar to those obtained for UKB, which we reiterate here for ease of comparison: mean r_g LDSC = 0.530; mean r_g GCTA–GREML = 0.502; proportion of genetic variance accounted for by PC1 LDSC = 62.17%; proportion of genetic variance accounted for by PC1 GCTA–GREML = 61.24%.

Using summary statistics from the above-described UKB analyses, we next created polygenic scores (PGS) for genetic *g* and the individual UKB cognitive traits and used them to predict, both individually and simultaneously, in Generation Scotland, variance in performance on the individual cognitive tests, the first unrotated principal component of all tests (to index phenotypic *g*), the first unrotated principal component of all tests except Mill Hill Vocabulary (to index a more fluid *g*) and educational attainment (Supplementary Table 7). Consistent with the above findings that individual cognitive outcomes are associated with a combination of genetic *g* and specific genetic factors, we observed a pattern in which many of the regression models that included both the PGS from genetic *g* and test-specific PGS were considerably more predictive of the cognitive phenotypes in Generation Scotland than regression models that included only either a genetic *g* PGS or a PGS for a single test. A particularly relevant exception involved the digit symbol substitution test in Generation Scotland, which is a similar test to the symbol digit substitution test in UKB for which we derived a PGS. We found that the proportional increase in R^2 in digit symbol by the symbol digit PGS beyond the genetic *g* PGS was <1%, whereas the genetic *g* PGS improved polygenic prediction beyond the symbol digit PGS by >100%, reflecting the power advantage obtained from integration of GWAS data from multiple genetically correlated cognitive traits using a genetic *g* model. An interesting counterpoint is the PGS for the VNR test, which is unique in the UKB cognitive test battery in partly indexing verbal knowledge[26,31]. Highlighting the role of domain-specific factors, a regression model that included this PGS and the genetic *g* PGS provided substantial incremental prediction relative to the genetic *g* PGS alone for those Generation Scotland phenotypes most directly related to verbal knowledge: Mill Hill Vocabulary (62.45% increase) and educational attainment (72.59%).

Discussion

Until now, research on the positive manifold of correlations among cognitive traits has been phenotypic in nature, or has made inferences regarding the roles of genes using twin approaches. Here we estimated and modelled the patterns of genetic sharing across diverse cognitive traits using genome-wide molecular data. Using data from seven different cognitive traits from UKB, we identified a positive manifold of genetic correlations. We found that a genetic *g* factor accounts for an average of about 58% (s.e. ≈ 5%) of the genetic variance in cognitive traits, with the proportion ranging widely (~9% to ~95%) across the traits. We went on to distil specific genetic loci broadly relevant for many cognitive traits via genetic *g* from those displaying patterns of more associations with the individual cognitive traits.

The importance of our results may be seen by contrasting the results of trails-B with RT. Analyses of multivariate genome-wide architecture indicated that, for trails-B, 95% of the genetic variance is accounted for by genetic *g* and only 5% is specific to trails-B. Moreover, all seven loci for trails-B have previously been reported in GWAS of other cognitive phenotypes (Supplementary Table 19), and four of these were implicated as relevant for genetic *g* at non-significant levels of heterogeneity. In contrast, for RT, analyses of multivariate genome-wide architecture indicated that 9.5% of the genetic variance is accounted for by genetic *g* while 90.5% of the genetic variance is specific to RT. Many of the 39 loci associated with RT have not been found in univariate GWAS of other cognitive traits (Supplementary Tables 17 and 24), and only four were implicated as relevant for genetic *g* at non-significant levels of heterogeneity. Therefore, when identifying loci associated with performance on an individual cognitive test, it is essential to know the extent to which its associations are broadly related to genetic *g* or specifically related to the phenotype under investigation.

Failure to take the multivariate structure of cognitive traits into account may lead to incorrect inferences[24]—either that discoveries made in a univariate GWAS of a cognitive trait are generalizable to the broader universe of cognitive traits when they are in fact specific to that trait, or that discoveries made in a univariate GWAS of a cognitive trait are specific to that trait when they are in fact broadly associated with all traits that load on genetic *g*. For instance, our multivariate analysis using GenomicSEM indicates that a locus on chromosome 7 (chr7:104558814–104588161) is associated with

genetic *g*. Similarly, we report an association of a locus on chromosome 8 (chr8:64496159–64842662) with trails-B (an index of executive function, which is itself strongly genetically correlated with *g*[14]) in the univariate GWAS, and our GenomicSEM analysis indicates that this locus is also related to genetic *g*. Lee et al.[32] have previously reported both of these loci as being associated with maths ability (Supplementary Table 22), but there are no previously reported associations with general cognitive function or intelligence. The current results indicate that the loci are broadly relevant to many abilities via genetic *g*, not simply to maths ability. Multivariate methods, such as that pioneered here, are necessary to distinguish whether a locus is narrowly relevant for an individual cognitive trait or broadly relevant to genetic *g*.

Genetic *g* was highly, but imperfectly, genetically correlated with previous univariate GWAS of general cognitive function and intelligence. Moreover, genetic *g* displayed lower (albeit still sizeable) genetic correlations with educational attainment than have previous univariate GWAS of general cognitive function and intelligence. This pattern suggests that previous GWAS of general cognitive ability might have tapped more academic forms of cognitive function (that is, crystallized abilities such as verbal knowledge) than those tapped by the present group of cognitive tests. Consistent with this hypothesis, a version of genetic *g* that excluded speeded tests—which are known to be among the most culturally decontextualized of the cognitive traits[42]—produced somewhat higher genetic correlations with educational attainment, though these continued be lower than those found between educational attainment and the previous univariate GWAS of general cognitive function and intelligence. A priority for future research will be to distinguish between genetic correlates of cognitive abilities that are driven by forms of higher-order thinking and academic knowledge from those that are driven more so by forms of arguably more basic neurocognitive processing[43]. Moreover, given that the phenotypic *g* values from different cognitive test batteries administered to the same sample correlate very highly[6], it will be useful in future research to discover whether genetic *g* values obtained from different test batteries also have very high correlations. The advantage of modern genomic methods, such as those used here, is that it is not necessary for the same sample to be tested on both batteries, or even on the same tests within a given battery[25].

Some researchers have adroitly argued that a positive manifold of test intercorrelations may, in principle, arise from a pattern in which individual genetic loci, biological mechanisms or cognitive processes contribute to subsets of traits, with the subsets varying across loci, mechanisms or processes[44–46]. Others have similarly argued that positive test intercorrelations may arise from reciprocal causation among abilities, or between abilities and external forces, and that genetic effects enter through specific points in the system and come to be correlated through dynamic propagation[47–49]. Here we have provided evidence not only of a positive manifold of genetic correlations at the aggregate, genome-wide, level of analysis, but also at the level of individual loci. Although these discoveries are themselves insufficient for determining the causes of the positive manifold, they do help to inform and constrain past and future accounts of the positive manifold and of the heritability of cognitive abilities.

It is important to consider this work in light of its key limitations. First, we had measures of different hierarchically intermediate traits (for example, processing speed, memory, reasoning), but we did not have multiple measures per intermediate trait. We were therefore unable formally to model genetic associations with intermediate traits as separate from those on *s* factors specific to the individual cognitive traits. In other words, based on the data currently available, we have been well positioned to discriminate between genetic loci that are broadly relevant for genetic *g* from those that display more heterogeneous patterns of relations with individual cognitive tests, but we are unable to distinguish loci relevant for very narrow traits captured by individual tests from those relevant to intermediately broad traits. Future work that employs a denser battery of cognitive tests will be valuable for such discernment. Second, using data from Generation Scotland, we closely replicated the positive manifold of genetic correlations observed in UKB and we demonstrated the utility of polygenic scores for genetic *g* constructed on the basis of the UKB data, but Generational Scotland was not sufficiently powered to conduct individual SNP-level analyses. Several large-scale GWAS exist for intelligence, but UKB appears to be the only such large-scale dataset for which multiple tests spanning a broad range of cognitive traits is available. When large-scale datasets with multivariate cognitive data become available, it will be prudent to examine the replicability of the individual *g* and *s* loci identified here. Finally, our analyses were based exclusively on individuals of European ancestry residing in the United Kingdom. It may not be assumed that the results reported here will generalize beyond this population.

In summary, we have inferred a genetic *g* factor using molecular genetic data, and we have discerned genetic loci that are associated with genetic *g* from those associated with more specific cognitive traits. We emphasize the large extant explanatory gap between genetic variation and shared (that is, general) variation in cognitive abilities.

Methods

Sample. Data from the UKB study were used for the present study (https://www.ukbiobank.ac.uk/). The UKB is a biomedical prospective cohort study that collected a wide range of genetic and health-related measures from a national sample of community-dwelling participants in the United Kingdom. Ethical approval for the UKB was granted by the Research Ethics Committee (no. 11/NW/0382). This study uses European ancestry genome-wide genotyped data from seven cognitive tests of varying sample size across phenotypes. Individuals were removed sequentially based on non-British ancestry, high missingness, high relatedness (samples with over ten putative third-degree relatives) and sex/gender mismatch between self-reported and genetic data. Our analysis sample included 332,050 unrelated participants of European descent with high-quality genotyping. Participant age ranged approximately 40–70 years at first assessment, and approximately 45–75 years at later assessments in which further cognitive tests were administered. For each cognitive test, we included no more than one test administration per participant in analyses.

Cognitive tests. Reaction time ($n = 330{,}024$): this test was self-administered by participants at the baseline UKB assessment. In this task, pairs of either identical or different cards were presented on a computer screen. If the two cards were identical, participants had to push a button as quickly as possible. Reaction time (RT) score corresponded with the time, in milliseconds, to identification of matching cards in four trials. Participants were presented with 12 trials in total. The first five trials were used as a practice. Of the remaining seven trials, four presented identical cards. The score is the mean time (in milliseconds) for these four trials. Whereas there were only a few trials, internal consistency is good (Cronbach $\alpha = 0.85$). Scores were multiplied by −1 such that higher scores indicated more optimal performance.

Matrix pattern recognition ($n = 11{,}356$): the non-verbal fluid reasoning matrix pattern recognition test is an adaptation of the matrices test included in the COGNITO battery[50], which is similar to the well-known Raven's progressive matrices test. This test was self-administered during the assessment centre imaging visit. This test involves the inspection of an abstract grid pattern with a piece missing in the lower right-hand corner. The pattern has a logical order. The participant is asked to select the correct multiple-choice option at the bottom of the screen to complete the logical pattern both horizontally and vertically. This 15-item test aims at assessing the ability to solve non-verbal, non-numerical problems using novel and abstract materials. The score is the total number of items solved correctly in 3 min.

Verbal numerical reasoning ($n = 171{,}304$): at the baseline assessment centre visit, a subsample of UKB participants self-administered the verbal numerical reasoning test. Participants were asked 13 multiple-choice questions that assessed verbal and numerical problem solving. The score was the number of questions answered correctly in 2 min. This test has been shown to have adequate test–retest reliability ($r = 0.65$)[51] and internal consistency (Cronbach $\alpha = 0.62$)[31]. The verbal numerical reasoning test was also administered to three subsamples of participants at the first repeat assessment visit, the assessment centre imaging visit and during the web-based cognitive assessment. In the web-based version of this test, because there was an additional question the maximum score was 14. In the current analysis the verbal numerical reasoning score used is taken from the first testing occasion for each participant.

Symbol digit substitution ($n = 87{,}741$): the symbol digit substitution test was self-administered during both the assessment centre imaging visit and the web-based cognitive assessment. Participants were shown a key, pairing shapes with numbers. Participants were asked to use the key to fill the maximum number of empty boxes with the corresponding number paired with shapes in a series of rows. The score is the number of correct symbol–digit matches made in 60 s. Those with a score coded as 0 and those with a score >70 had their score set to missing. In this analysis, the scores used were from the first testing occasion for each participant.

Memory pairs-matching test ($n = 331{,}679$): at the baseline UKB assessment, memory was measured using a 'pairs-matching task'. In this self-administered task, participants are shown a randomly arranged, 4×3 grid of 12 'cards', with six pairs of matching symbols, for 5 s. The symbols were then hidden and the participant was instructed to select, from memory, the locations of the pairs that matched, in the fewest possible number of attempts. There was no time limit for this task. The memory score was the total number of errors made during this task before all pairs were identified. Scores were multiplied by −1 such that higher scores indicated more optimal performance.

Tower rearranging ($n = 11{,}263$): this test was self-administered during the imaging assessment centre visit. It is similar to the well-known 'tower of Hanoi' task. Participants were presented with a display (display A) containing three different coloured hoops arranged on three pegs (towers). Another display (display B) was shown underneath display A, with the three hoops arranged differently. The task involves deciding how many moves it would take to change display A into display B. The score was the number of correctly completed trials achieved in 3 min.

Trail making test-B ($n = 78{,}547$): this test is a computerized version of the Halstead–Reitan trail-making test[52]. The trail-making test was self-administered during both the assessment centre imaging visit and the web-based cognitive assessment. In part B of the test, participants were presented with the numbers 1–13 and the letters A–L arranged quasi-randomly on a computer screen. The participants were instructed to switch between touching the numbers in ascending order, and the letters in alphabetical order (for example, 1-A-2-B-3-C) as quickly as possible. The score was the time (in seconds) taken to successfully complete the test. Those with a score coded as 0 (denoting trail not completed) had their score set to missing. Scores were multiplied by −1 such that higher scores indicated more optimal performance. In this analysis, the scores used were from the first testing occasion for each participant.

Genotyping. Prior to release of the UKB genetic dataset, quality control measures were applied; these are described in Bycroft et al.[53]. Imputed dosage scores on up to 80,639,280 autosomal variants were analysed (imputation reference panels included UK10K haplotype, 1000 Genomes Phase 3 and Haplotype Reference Consortium panels); all variants had a minor allele frequency ≥0.000009 and an imputation quality (INFO) score of >0.6.

Genome-wide association analyses. Univariate genome-wide association analyses were performed for covariate-residualized scores on each UKB cognitive phenotype using a linear association test in BGENIE[53]. The covariates were age, assessment centre (where relevant), genotype batch, array and 40 genetic principal components. For phenotypes collected across multiple testing occasions, a separate GWAS was performed for non-overlapping participants from each occasion and an inverse-variance-weighted meta-analysis was implemented in METAL[54]. Because the size of the subsets of individuals for each phenotype varies greatly, an additional quality control filter to remove SNPs with a minor allele count <25 was applied to all GWAS summary results before further analyses.

Factor models. We performed genetic factor analysis on the UKB cognitive phenotypes with Genomic SEM[25], and phenotypic factor analysis with the lavaan package for R[55]. In both genetic and phenotypic factor analysis, a common factor model specifies that k phenotypes are described as linear functions of a smaller set of m (continuous) latent variables: $\mathbf{y} = \Lambda\boldsymbol{\eta} + \boldsymbol{\varepsilon}$. In this equation, $\mathbf{y}$ is a $k \times 1$ vector of indicators, $\boldsymbol{\varepsilon}$ is a $k \times 1$ vector of residuals, $\boldsymbol{\eta}$ is an $m \times 1$ vector of common factors and Λ is a $k \times m$ matrix of factor loadings—that is, regressions relating the common factors to the set of indicators. In the genetic factor model, $\mathbf{y}$ represents the genetic components of the GWAS phenotypes whereas, in the phenotypic factor model, $\mathbf{y}$ represents the phenotypes themselves. The model-implied covariance matrix of a confirmatory factor analysis is $\Sigma(\theta) = \Lambda\Psi\Lambda' + \Theta$, where Ψ is an $m \times m$ latent variable covariance matrix (in the case of a single common factor, Ψ is simply equal to the variance of the factor which we fix at 1 for scaling identification purposes), and Θ is a $k \times k$ matrix of covariances among the residuals, $\boldsymbol{\varepsilon}$ (typically a diagonal matrix, to indicate that all indicator residuals are assumed to be independent of one another). A set of parameters (θ) is estimated such that the fit function indexing the discrepancy between the model-implied covariance matrix, $\sum(\theta)$, and the empirical covariance matrix, S, is minimized.

For genetic factor modelling in Genomic SEM[25], S is a genetic covariance matrix estimated using a multivariable extension of LDSC[27]. For phenotypic factor modelling in lavaan, S is a phenotypic covariance matrix that is empirically estimated from the raw phenotypic data using full-information maximum-likelihood estimation. For genetic factor modelling in Genomic SEM, the fit function used to estimate the model parameters takes into account the precision of the elements of the S matrix, along with their sampling dependencies (which are needed to appropriately account for sample overlap across the GWAS phenotypes) in the form of a sampling covariance matrix, V, that is estimated using a jackknife resampling procedure in the multivariable extension of LDSC available in Genomic SEM. Model fit is considered good when $\sum(\theta)$ closely approximates S. For Genomic SEM, the fit function used was diagonally weighted least squares, with a sandwich correction to adjust standard errors of model parameters based on the off-diagonal elements of V. For phenotypic modelling, the fit function used was maximum likelihood.

In Genomic SEM, goodness-of-fit of the model is assessed by means of the SRMR, model χ^2, Akaike information criterion and CFI. For phenotypic factor modelling, we additionally consider RMSEA. Hu and Bentler[56] have proposed the following criteria for a good fit: CFI > 0.95, RMSEA < 0.08.

Estimation of SNP-based heritability and genetic correlations using GCTA–GREML. Our primary means of estimating the UKB cognitive phenotype SNP-based heritability and genetic correlations was with the multivariable version of LDSC available in Genomic SEM, as described in the "Factor models' section. However, to verify that the estimated genetic correlation matrix was consistent across estimation methods reliant on different assumptions, we additionally implemented GCTA–GREML to estimate SNP-based heritability[29] and genetic correlations[28]. Due to computational requirements for the bivariate GCTA–GREML analyses, a subset of individuals was created and used for all GCTA–GREML analyses. This subset was created by performing listwise deletion for RT, memory, VNR, symbol digit substitution and trails-B ($n = 72{,}583$). The same covariates were included in all GCTA–GREML analyses as for the SNP-based association analyses. One individual was excluded from any pair of individuals with an estimated coefficient of relatedness of >0.05.

Genetic correlations with neural phenotypes and longevity. We extended the factor models in Genomic SEM to estimate the genetic correlations between the genetic g factor from the UKB cognitive phenotypes and each of nine collateral phenotypes in turn: educational attainment[32]; general cognitive function from Davies et al.[19], Savage et al.[21] and Hill et al.[20]; total brain volume from UKB[37]; and Alzheimer's disease[34], schizophrenia[35], ADHD[36], autism spectrum disorder (ASD)[57] and longevity[38].

Multivariate GWAS in Genomic SEM. Using the univariate summary statistics for each of the seven UKB cognitive phenotypes, Genomic SEM[25] was used to conduct a multivariate GWAS, with the genetic g factor as the GWAS target (see left-hand portion of Supplementary Fig. 9). Because the typical unit variance scaling cannot be directly specified in a model in which the latent factor is a dependent variable, we specified unit loading scaling (with matrices as the reference indicator; Supplementary Table 29). Genomic SEM provides a SNP-specific heterogeneity statistic, Q, which indexes the extent to which the specified factor model is insufficient to account for the SNP effects on the individual traits analysed. High Q values for a given SNP indicate that a model that estimates SNP associations with each individual trait (see right-hand portion of Supplementary Fig. 9) fits better than a model that estimates a single SNP association with the factor. In other words, SNPs with genome-wide significant Q values may be interpreted as SNPs that do not affect the genetic g. A detailed explanation of the Q statistic is provided in the Supplementary Information (Interpreting the heterogeneity statistic).

For multivariate GWAS in Genomic SEM, summary statistics for individual tests were restricted to SNPs with a minor allele frequency (MAF) > 1% and INFO score >0.6, and to SNPs that were present for all seven cognitive tests. The summary statistics were also filtered to SNPs present in the European-only 1000 Genomes Phase 3 reference panel, because the SNP minor allele frequencies from the reference panel are necessary to obtain their variance for inclusion in the genetic covariance (S) matrix. Using these quality control steps, 7,857,346 SNPs were present across all seven cognitive tests. Note that all cognitive phenotypes had already been residualized for covariates when conducting the univariate GWAS, summary statistics for which are entered into multivariate analyses within Genomic SEM such that further covariate adjustment was not needed at this stage.

We adopt the field standard alpha threshold of 5×10^{-8} for GWAS. This threshold amounts to a Bonferroni correction for the theoretical number of independent tests in the genome given known linkage disequilibrium structure[58]. Because all seven phenotypes are highly genetically correlated, it is inappropriate to perform an additional Bonferroni correction for the seven additional phenotypes, and we do not focus our interpretation on results of the seven univariate GWAS. Rather, we focus on results of the multivariate GWAS within Genomic SEM for which there are two families of theoretical tests, each constituting a single set of GWAS-type statistics: (1) genome-wide SNP associations with genetic g and (2) genome-wide SNP-specific heterogeneity indices (Q).

Genome-wide significant loci using functional mapping and annotation of genetic associations (FUMA). Genome-wide significant loci were defined from the SNP-based association results using FUMA[59]. The SNP2GENE function was

used to identify independent significant SNPs, defined as those with $P \leq 5 \times 10^{-8}$ and independent of other genome-wide significant SNPs at $r^2 < 0.6$. Tagged SNPs, for use in subsequent annotations, were then identified as all SNPs with MAF ≥ 0.0005 and that were in linkage disequilibrium of $r^2 \geq 0.6$ with at least one of the independent significant SNPs. These tagged SNPs included those from the 1000 Genomes reference panel, and need not have been included in the GWAS performed in the current study. Genome-wide significant loci that were 250 kb or closer were merged into a single locus. Lead SNPs were defined as independent significant SNPs that were independent from each other at $r^2 < 0.1$. We performed look-ups on all tagged SNPs ($r^2 > 0.6$) within each locus, including all 1000 Genomes SNPs; previously reported genome-wide significant findings are detailed in Supplementary Tables 22–28.

Polygenic prediction. Generation Scotland: the Scottish Family Health Study (GS) is a family-structured, population-based cohort study recruited between 2006 and 2011. Participant recruitment occurred in Glasgow, Tayside, Ayrshire, Arran and Northeast Scotland, yielding a total sample size of 24,084 with an age range of 18–100 years, and up to four generations per family, of which we selected one participant per family. A full cohort description is provided elsewhere[40,41] and online at http://www.generationscotland.org/. Ethical approval for GS was obtained from the Tayside Committee on Medical Research Ethics (on behalf of the National Health Service). Genotyping, using the Illumina HumanOmniExpressExome-8 v.1.0 chip, was performed at the Edinburgh Clinical Research Facility, University of Edinburgh[60]. Participants were removed from GS if they had contributed to both GS and UKB ($n = 622$). For PGS analyses, 6,950 unrelated GS participants were retained.

The cognitive measures available in GS were Wechsler Logical Memory (episodic memory), Mill Hill Vocabulary (crystallized knowledge), Wechsler Digit Symbol Substitution (processing speed) and Verbal Fluency (semantic fluency), as described previously[40,41]. We created a phenotypic *g* using the first unrotated principal component of the cognitive measures, and also a fluid *g* using the first unrotated principal component of the cognitive measures excluding the Mill Hill Vocabulary scores.

Polygenic scores were created using PRSice v.2 (https://github.com/choishingwan/PRSice) using a prespecified *P* value threshold of 1.0—that is, all SNPs[61]. Summary results from the genetic *g* and univariate cognitive test GWAS were used to create PGS for the GS individuals. Before creating these scores, SNPs with MAF < 0.01 were removed and clumping was used to obtain SNPs in linkage disequilibrium with $r^2 < 0.25$ within a 250-kb window. Polygenic scores for the individual cognitive tests were created using all available SNPs from the GWAS summary results. For genetic *g*, all SNPs located within significant *Q* loci were removed from the GWAS summary results before the creation of profile scores.

Linear regression models were used to examine the associations between polygenic scores and cognitive performance and educational attainment in GS. All models included age at measurement, sex and ten genetic principal components, to adjust for population stratification. We created regression models fitting each polygenic score individually, a multivariate model including all eight polygenic scores (genetic *g*, RT, memory, matrix, symbol digit substitution, trail-B and tower rearranging) and a series of models that fitted the genetic *g* polygenic score plus one individual cognitive test score. From these models we were able to determine the contributions of genetic *g* and each individual UKB cognitive test to prediction of variance in cognitive performance and educational attainment in an independent sample, GS.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Complete summary GWAS results from this paper are available at https://www.lothianbirthcohort.ed.ac.uk/content/summary-data-and-other-resources. Raw data for UKB can be requested at https://www.ukbiobank.ac.uk/register-apply/. Raw data for Generation Scotland can be requested at https://www.ed.ac.uk/generation-scotland/for-researchers/access-to-resources/access.

Code availability

Code to perform common factor modelling and multivariate GWAS within Genomic SEM can be found at https://github.com/MichelNivard/GenomicSEM/wiki.

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Author contributions

I.J.D. and E.M.T.-D. jointly conceived of the idea, designed the study and formulated the analytic plan. J.F. and G.D. performed the analyses, with contributions from A.D.G. I.J.D. and E.M.T.-D. wrote the paper, with contributions from J.F. and G.D. All authors contributed to editing the paper.

Competing interests

I.J.D. is a participant in UKB. All other authors declare no competing interests.

Additional information

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Sampling strategy	We did not collect the data as part of this study. Data were made available to us for secondary data analysis by the UK Biobank and Generation Scotland lead investigators.
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Non-participation	We did not collect the data as part of this study. Data were made available to us for secondary data analysis by the UK Biobank and Generation Scotland lead investigators.
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