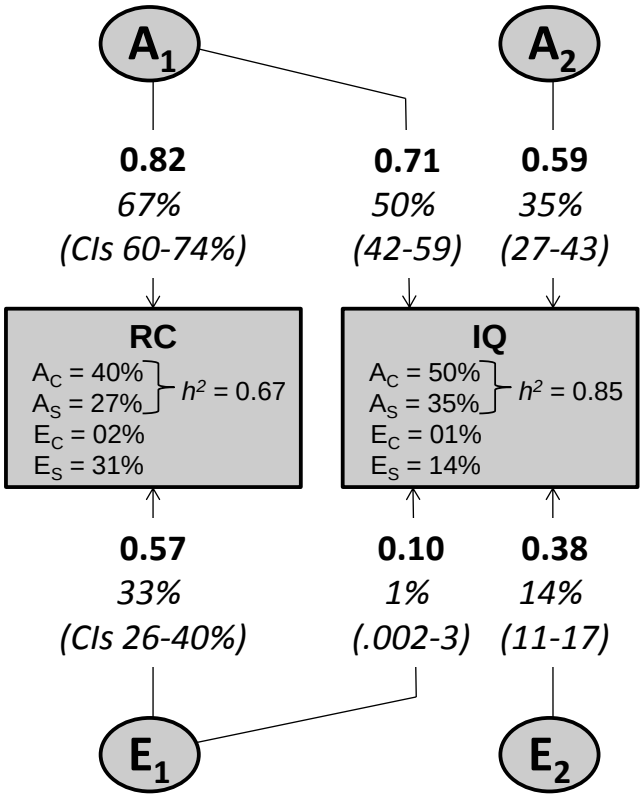

Figure S1. Bivariate Cholesky Decomposition: RC, IQ. This Cholesky decomposition [1] details the genetic and environmental overlap between a Relational Complexity principal component (RC) and IQ. Cholesky decomposition shows that the RC component was more heritable than the individual RC tasks (0.67 vs. 0.41-0.57), but less heritable than the latent relational processing factor (0.67 vs. 0.86) (Figure 2). IQ was strongly heritable (0.85) and there was considerable genetic overlap between the RC and IQ, such that 60% of genetic variance in RC (40/67) and 59% of the genetic variance in IQ (50/85) is estimated to come from a common genetic source. Even so, this shows that both RC and IQ retain a similar and substantial degree of genetic independence (i.e. 40% for RC (27/67), 41% for IQ (35/85)). In contrast to the genetic overlap almost none was found for unique environmental sources of influence. (As Cholesky decomposition only identifies specific influences for the last variable, we ran two bivariate analyses that allowed both RC and IQ to be the last variable, thus allowing both common (A_C, E_C) and specific (A_S, E_S) influences to be identified for both variables.) Overall, this model shows that genes account for most of the correlation (i.e. 91% (0.82x0.71/((0.82x0.71)+(0.57x0.10))) between RC and IQ.

References

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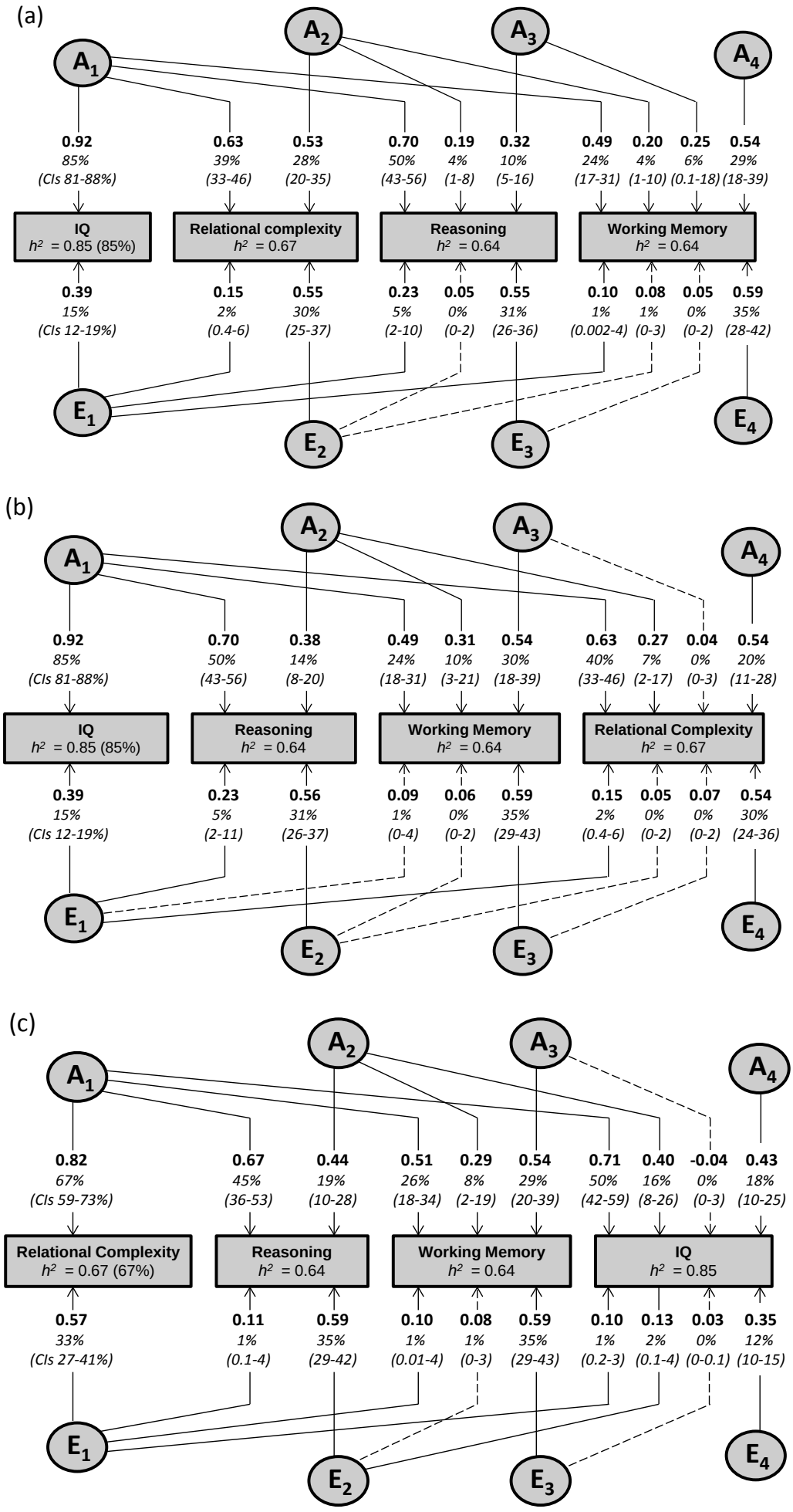


Figure S2. Quadrivariate Cholesky Decomposition: Alternative Variable Orders. These path diagrams show **(a)** reverse order for RC and IQ, **(b)** RC as the last variable, and **(c)** IQ as the last variable. Reversing the order of RC and IQ **(a)** shows that RC accounts for 8% of the covariation between reasoning and working memory independently of IQ (compared to IQ accounting for 12% independently of RC). Having RC and IQ as the last variable shows their genetic independence from the other variables. For RC **(b),** 30% of total genetic variance (20/67) is independent of sources influencing IQ, reasoning, and working memory. For IQ **(c)** 21% of total genetic variance (18/85) is independent of RC, reasoning and working memory. This last estimate is likely artificially reduced due to a common test (Arithmetic) contributing to both reasoning and IQ.

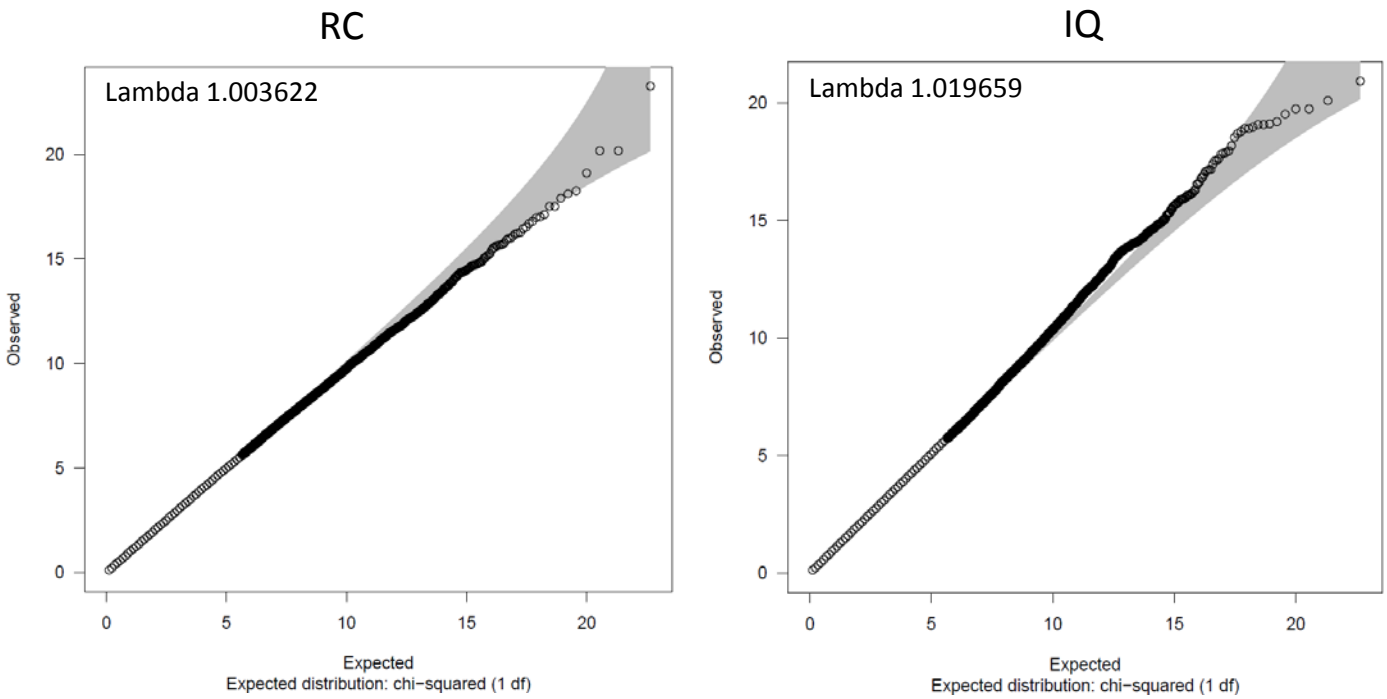
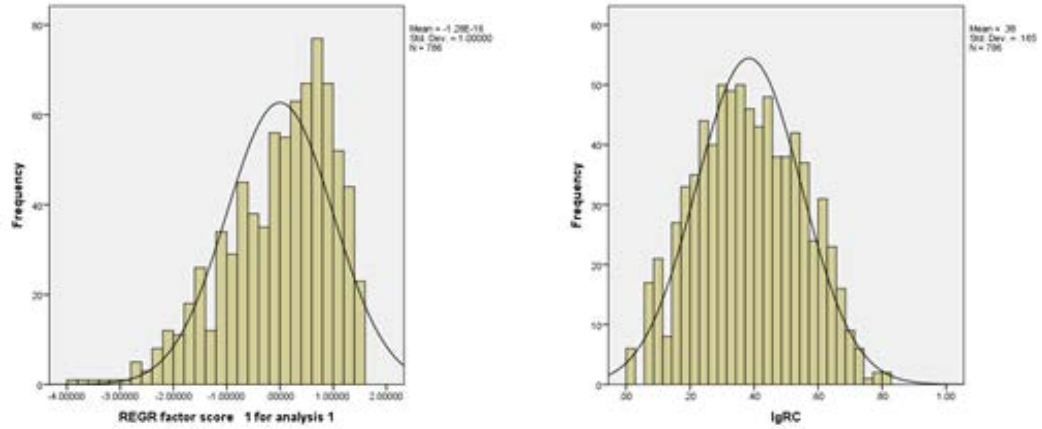


Figure S2. QQ plots for Relational Complexity (RC) and IQ show no evidence of population stratification, withLambda values indicating no inflation of association signal.

Table S1. Methods: Discovery Sample Genotyping and Preliminary Analyses

Zygosity and Genotyping	Zygosity was determined from DNA using a commercial kit (AmpFlSTR Profiler Plus Amplification Kit, ABI) and was later confirmed in those genotyped. DNA samples were genotyped using the Illumina 610-Quadv1 whole-genome SNP array (San Diego, California) as described in detail elsewhere (20). Briefly, SNPs (total of 516,133) were filtered to have a mean GenCall score ≥ 0.7, call rate ≥ 95%, a minor allele frequency (MAF) ≥ 1%, and Hardy-Weinberg Equilibrium (HWE) ≥ 10^{-6}.
Data Transformation (in SPSS)	RC, N-term, latin square, and sentence comprehension were transformed to reduce negative skew using IBM SPSS Statistics Version 19. They were log transformed ($\log_{10}$(K-X), where K was a constant from which each score was subtracted so that the smallest score was 1 and X was the score), with the exception of Sentence Comprehension, which was square root transformed (sqrt(K-X)). IQ, working memory, and reasoning were normally distributed. Distributions for the RC component before and after transformation: 
Modelling of Data (in Mx)	Modelling of raw data was performed in Mx using a full information maximum likelihood (FIML) estimator, which uses all data points regardless of missingness [1]. The fit of constrained models was compared to the full model by examining the difference in the -2 log likelihood, which is distributed as a chi-square for given degrees of freedom.
Assumption Testing (in Mx)	We assessed homogeneity of sampling by examining the means and variances for birth order and zygosity effects as described in McGregor et al. [2]. Note that for those twins who were not genome-scanned, zygosity was determined using a commercial kit (AmpFISTR Profiler Plus Amplification Kit, ABI).
Sex and Age Effects (in Mx)	The effects of sex and age were assessed by comparing the fit of models that either included, or excluded, them as covariates. Significant covariates were included in further modelling.
Test-retest Reliability (in Mx)	To examine test-retest reliability, data were collapsed over birth order and zygosity.
Twin Correlations (in Mx)	We tested if twin correlations for males and females could be set equal for (1) MZ and (2) DZ pairs. If not, this is suggestive of *magnitude* differences in genetic and/or environmental estimates for boys and girls. Similarly, if correlations for opposite-sex DZ pairs are significantly lower than those of same-sex DZ pairs, this indicates different *sources* of influence between boys and girls. Where DZ (and MZ) correlations could be set equal for males and females, and further, where opposite-sex DZ correlations could be set equal to same-sex DZ correlations, then further analyses were run with one MZ and one DZ group.
Significance levels (GWA and VEGAS) adjusted for correlated traits.	Significance levels for genome-wide association (GWA) and gene-based analyses (VEGAS) were adjusted for testing two correlated traits as per matSpD (http://gump.qimr.edu.au/general/daleN/matSpD). For GWA, the corrected threshold was 3.1×10^{-8} (standard threshold = 5.0×10^{-8}). For VEGAS, the threshold after correcting for 17,668 genes (0.05/17,688) and two correlated traits was 1.7×10^{-6}.

NOTE: RC = Relational Complexity, MZ = monozygotic, DZ = dizygotic

References

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2. McGregor B, Pfitzner J, Zhu G, Grace M, Eldridge A, et al. (1999) Genetic and environmental contributions to size, color, shape, and other characteristics of melanocytic naevi in a sample of adolescent twins. Genetic Epidemiology 16: 40-53.

Table S2. Results for Assumption Testing and Sex and Age Effects.

Analyses	**Details**
Assumption Testing	No birth order or zygosity effects were found for any measure for means or variances ($\Delta\chi^2_4$ ranged 0.4-4.1 for birth order, $\Delta\chi^2_2$ ranged 0.04-1.5 for zygosity), with the exception of a variance difference for zygosity found for Reasoning ($\Delta\chi^2_2 = 8.6$), where female DZ pairs had low variability (0.66-0.69) compared to male and female MZ pairs and male DZ pairs (0.91-1.00). As a consistent zygosity effect across both males and females was not found, variances for female MZ and DZ pairs were set to be equal. Means and variances for non-twin siblings could be set equal to those of twins for all measures except the Sentence and N-term Tasks, where for males only, non-twin siblings had higher means than twins (18.2 vs 16.8, $\Delta\chi^2_2 = 8.1$ and 13.3 vs 12.0, $\Delta\chi^2_2 = 10.4$ respectively). Means for these measures were left free to vary between non-twin siblings and twins in further analyses. The differences found may reflect a sampling issue due to the small number of males in the non-twin sibling group (33 males vs. 67 females - note that 3rd born DZ triplets are grouped with non-twin siblings in analyses, as the genetic relationship is the same).
Sex and Age Effects	Means and variances could be set equal for males and females for all measures except IQ and Reasoning, where means differed significantly ($\Delta\chi^2_1 = 22.2$ and 12.6 respectively). On average, males had higher IQ scores than females (M = 113.9 vs. 108.7) and higher Reasoning scores (factor z-score M = 0.14 vs. -0.11). Consequently, sex was included as a covariate in further analyses. No effects for age were found ($\Delta\chi^2_1$ ranged 0.1-2.4).

Table S3. Sample and Analyses Details for the Replication Cohorts

English (Avon Longitudinal Study of Parents and Children (ALSPAC))	
Sample	**This Study:** 4078 unrelated adolescents (47.4% male) aged 14-17 years (*M* = 15.4±0.3). **Full Study Numbers:** ALSPAC recruited 14,541 pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992. 14,541 is the *initial* number of pregnancies for which the mother enrolled in the ALSPAC study and had either returned at least one questionnaire or attended a "Children in Focus" clinic by 19/07/99. Of these *initial* pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of **new pregnancies** not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 18 is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrolment are described in more detail in the cohort profile papers: 1) Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: The 'Children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children Int J Epidemiol. 2013 Feb;42(1):111-27. PMID: 22507743 <http://ije.oxfordjournals.org/content/early/2012/04/14/ije.dys064.full.pdf+html>. 2) Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, Ring S, Nelson SM, Lawlor DA. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. Int J Epidemiol. 2013;42(1)97-110. PMID: 22507742 http://ije.oxfordjournals.org/content/42/1/97.full.pdf+html The total sample size for analyses using any data collected after the age of seven is therefore 15,247 pregnancies, resulting in 15,458 fetuses. Of this **total sample** of 15,458 fetuses, 14,775 were **live births** and 14,701 were **alive at 1 year of age**. A 10% sample of the ALSPAC cohort, known as the **Children in Focus (CiF) group**, attended clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The CiF group were chosen at random from the last 6 months of ALSPAC births (1432 families attended at least one clinic). Excluded were those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study of infant development in Avon.
Genotyping (of the children)	A total of 9912 subjects were genotyped using the Illumina HumanHap550 quad genome-wide SNP genotyping platform by 23andMe subcontracting the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, NC, USA. Individuals were excluded from further analysis on the basis of having incorrect gender assignments; minimal or excessive heterozygosity (<0.320 and >0.345 for the Sanger data and <0.310 and >0.330 for the LabCorp data); disproportionate levels of individual missingness (>3%); evidence of cryptic relatedness (>10% IBD) and being of non-European ancestry (as detected by a multidimensional scaling analysis seeded with HapMap 2 individuals, EIGENSTRAT analysis revealed no additional obvious population stratification and genome-wide analyses with other phenotypes indicate a low lambda). The resulting data set consisted of 8365 individuals. SNPs with a minor allele frequency of <1% and call rate of <95% were removed. Furthermore, only SNPs which passed an exact test of Hardy–Weinberg equilibrium (P>5×10-7) were considered for analysis. After quality control, 8365 unrelated individuals, who were genotyped at 500527 SNPs, were available for analysis. EIGENSTRAT principal components analysis was used to generate the top 100 principal components after the removal of known regions of long linkage disequilibrium in the data [1,2]. Known autosomal variants were imputed with MACH 1.0.16 Markov Chain Haplotyping software [3,4], using CEPH individuals from phase 2 of the HapMap project (HG18) as a reference set (release 22). For the X chromosomal variants, imputation was performed using MiniMac (v 4.43) [5] and CEPH individuals from phase 3 of the HapMap project (HG18) were used as the reference set.
Ethical Approval	Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.
Current Cohort	The cohort examined in the current study participated in the Teen Focus 3 (TF3) clinic conducted from October 2006 to November 2008, when they were aged from 14.3 to 17.7 years (*M*=15.5). There were 5515 participants in TF3, of whom 4078 had both genotyping and the phenotypes of interest.
Phenotypes Examined	Matrix Reasoning: a subtest of the WASI [6], and IQ: derived from the WASI subtests (Vocabulary, Similarities, Block Design, and Matrix Reasoning - note that IQ and Matrix Reasoning are not independent. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).
Analyses	Sex, age, and 10 ancestry principal components were included as covariates in all analyses. SNP-based analyses of association were performed in PLINK [7] for 11 target SNPs as well as SNPs located in the genes *NPS* (55 SNPs) and *FAM105A* (30 SNPs). P-values obtained for the SNPs in the two genes were used to run gene-based analyses with the software VEGAS [Versatile Gene-Based Association Study; 8] to derive gene-based p-values.
Scottish Cohort (Lothian Birth Cohort 1936 (LBC1936))	
Sample	This sample is the University of Edinburgh-based Lothian Birth Cohort of 1936 [9]. Most of the participants undertook a general intelligence test (Moray House Test No. 12) at age 11 years and were recruited for this

	cohort at a mean age of 70. Assessments have been in three waves (Wave 1: mean age = 70 years; Wave 2: mean age =73; Wave 3: mean age = 76). In total, 1091 participants joined the LBC1936 and were assessed at Wave 1 (548 men, 543 women) for cognitive ability and other attributes. Both the phenotypes of interest and genotypes were available for 986-1001 individuals (varying with phenotype).
Phenotype Data	The phenotypes of interest were reasoning (Matrix Reasoning from the Wechsler Adult Intelligence Scale-III UK), working memory (Letter Number Sequencing from the WAIS-III UK), and general cognitive ability, or IQ (Moray House Test).
Genotyping	DNA was extracted from blood samples and SNP genotyping was performed with the Illumina 610k Quad Bead chip either by the Wellcome Trust Clinical Research Facility in Edinburgh. Individuals were checked for disagreement between genetic and reported gender. Relatedness between subjects was investigated and, for any related pair of individuals, one was removed. Samples with a call rate ≤.95, and those showing evidence of non-caucasian descent, were also removed. SNPs were included in the analyses if they met the following conditions: call rate ≥.98, minor allele frequency ≥.01, and HWE test with P ≥.001.
Analyses	The single SNP analysis of 11 target SNPs and SNPs located in the genes *NPS* and *FAM105A* was performed in PLINK [7] using a linear regression additive model. All cognitive phenotypes were corrected for age, sex and four MDS components prior to the analysis. Seven subjects with outlying Moray House Test scores (Z< -3.5) were removed prior to the Moray House Test analyses. There were no Matrix Reasoning or Letter Number Sequencing outliers. The gene based analysis was performed in VEGAS [8].
Dutch Cohort (Netherlands Twin Registry (NTR))	
Sample & Phenotype Data	The phenotype data were collected as part of several different projects within the NTR [10-12], and consisted of summed scores on the Raven's Standard Progressive Matrices or Raven's Advanced Progressive Matrices, for 920 individuals from 340 families. 44.7% of the sample was male. The sample contained mostly children (N=737, age: M=14.5, SD=3.2) and some adults (N=183, age: M=43.8, SD=3.9). Seeing as the data originated from different projects (with measurements taking place at children's age 9, 12, 15, or 17), the Raven scores were standardized within each project (M=0, SD=1). Part of the sample was measured longitudinally (on 2 measurement occasions, 3 years apart); for these individuals, the standardized data were averaged over measurement occasions. Standardized Raven scores were used in all subsequent analyses.
Genotype Data	Blood and/or buccal samples for DNA extraction were collected as part of several projects within the NTR. Genotyping was performed using the Affymetrix Human SNP Array 6.0 at the Avera Institute, Sioux Falls, South Dakota, USA. Genotypes were called using the BIRDSEED V2 algorithm. Samples were selected if the CQC metric was above .4 (resulting in a call rate > 99%) and checked for Mendelian errors, excessive heterozygosity, ethnic outliers and discrepancies in relatedness and gender. For the present study, we selected 10 SNPs (rs4390263, rs12882037, rs3827183, rs11195283, rs2442756, rs1242923, rs4482248, rs12419146, rs7801010, and rs2964546 (genotyping was not available for rs10209999), and all available SNPs from 2 genes (*NPS* and *FAM105A*; 32 and 41 SNPs, respectively).
Analyses	All analyses were performed using sex, age, information on type of sample used for DNA extraction (blood/buccal), and 12 principal components (10 representing ancestry and 2 representing chip effects) as covariates. The SNP-based analyses were performed in Plink [7], using the --family option to control for family structure. For the SNPs residing on the two genes of interest, the SNP-based p-values obtained using Plink were subsequently used as input for VEGAS [8] to obtain gene-based p-values.
Norwegian Cohort (Norwegian Cognitive NeuroGenetics (NCNG))	
Sample	This sample was recruited through newspaper advertisements in the Oslo and Bergen urban areas and comprised 670 unrelated individuals aged 20-79 years (*M*=47.6±18.3) with mean IQ 119±10.6 [13]. All participants were interviewed and probed for past or present neurological or psychiatric diseases known to affect the central nervous system, and for history of substance abuse. Any person with a history of treatment for any of these conditions was excluded from the sample. Participants should have completed basic education with no history of learning deficits; persons who, after initial inclusion, on subsequent testing scored more than one standard deviation (*SD*) below their age norm on intelligence or memory were excluded. Furthermore, persons with a score on a depression inventory indicating a previously undiagnosed depressive illness were excluded. The participants were native speakers of Norwegian. All participants gave their informed consent for participation, which included donation of a blood sample, DNA extraction and genotyping, and storage of the remaining blood sample in a biobank. The recruitment procedure resulted in a cognitively normal sample, skewed towards the high functioning intelligence range.
Genotyping	DNA samples were freshly extracted from blood and genotyped on the Illumina Human610-Quad Beadchip. Quality control was performed with the iterative 'check.marker' function in the R package GenABEL [14]. Cryptic relatedness was assessed by identity-by-state (ibs), removing one sample from a pair with 'ibs.threshold' ≥ .85. Individualswith heterozygosity values greater than two *SD*s from the sample mean, or with unresolved sex discrepancies, were removed. Population structure was assessed by multidimensional scaling (MDS) analysis (100K random single nucleotide polymorphisms (SNPs), removing outlying samples with possible recent non-Norwegian ancestry. Finally, SNPs with a call rate < .95, minor allele frequency (MAF) < .01, and Hardy-Weinberg Equilibrium (HWE) exact test P < .001, were excluded. This resulted in a final dataset of 554,225 SNPs genotyped in a homogeneous Norwegian sample of 670 individuals [13].
Measures	Data collected from a broad battery of psychometric tests provided measures including IQ (obtained from Vocabulary and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence [WASI; 6]), reasoning (WASI Matrix Reasoning), working memory (Letter-Number Span, Digit Symbol), and processing speed (Digit Symbol) [13].

	Note that the reasoning measure is not independent of the score for IQ.
Analyses	Association analyses were performed using PLINK [7] for 11 target SNPs and SNPs located in the genes *NPS* and *FAM105A*. Sex and age were included as covariates for all traits with the exception of IQ, for which sex was the only covariate. Gene-based analyses were performed using VEGAS [8].

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Table S4. Univariate Cholesky Decomposition showing Additive Genetic (A), Common Environmental (C), and Non-shared Environmental Influences (E) (with 95% Confidence Intervals).

Model	-2LL	df	Δ-2LL	Δdf	AIC	A	C	E
Latin Square								
ACE	2188.9	781	-	-	626.9	0.44 (0.16, 0.55)	0.00 (0.00, 0.20)	0.56 (0.45, 0.69)
AE	**2188.9**	**782**	**0.0**	**1**	**624.9**	**0.44 (0.31, 0.55)**	-	**0.56 (0.45, 0.69)**
CE	2196.9	782	8.0	1	632.9	-	0.28 (0.18, 0.37)	0.72 (0.63, 0.82)
E	2230.5	783	41.6	2	664.5	-	-	1.00 (1.00, 1.00)
N-term								
ACE	2157.6	779	-	-	599.6	0.31 (0.00, 0.57)	0.16 (0.00, 0.40)	0.53 (0.42, 0.67)
AE	**2159.3**	**780**	**1.7**	**1**	**599.3**	**0.50 (0.39, 0.60)**	**-**	**0.50 (0.40, 0.61)**
CE	2161.0	780	3.4	1	601.0	-	0.37 (0.28, 0.45)	0.63 (0.55, 0.72)
E	2219.3	781	61.6	2	657.3	-	-	1.00 (1.00, 1.00)
Sentence								
ACE	2152.6	780	-	-	592.6	0.48 (0.18, 0.64)	0.06 (0.00, 0.29)	0.45, 0.36, 0.58)
AE	**2152.9**	**781**	**0.3**	**1**	**590.9**	**0.56 (0.45, 0.65)**	-	**0.44 (0.35, 0.55)**
CE	2161.8	781	9.2	1	599.8	-	0.38 (0.29, 0.46)	0.62 (0.54, 0.71)
E	2224.0	782	71.4	2	660.0	-	-	1.00 (1.00, 1.00)
Relational Complexity								
ACE	2110.2	779	-	-	552.2	0.61 (0.36, 0.75)	0.07 (0.00, 0.27)	0.32 (0.25, 0.42)
AE	**2110.6**	**780**	**0.4**	**1**	**550.6**	**0.68 (0.60, 0.75)**	**-**	**0.32 (0.25, 0.40)**
CE	2129.6	780	19.5	1	569.6	-	0.46 (0.38, 0.54)	0.54 (0.46, 0.62)
E	2224.5	782	114.3	2	662.5	-	-	1.00 (1.00, 1.00)
IQ								
ACE	1935.9	774	-	-	387.9	0.72 (0.54, 0.87)	0.12 (0.00, 0.30)	0.16 (0.12, 0.20)
AE	**1937.4**	**775**	**1.5**	**1**	**387.4**	**0.84 (0.80, 0.88)**	**-**	**0.16 (0.12, 0.20)**
CE	1993.1	775	57.2	1	443.1	-	0.62 (0.55, 0.68)	0.38 (0.32, 0.45)
E	2180.2	776	244.3	2	628.2	-	-	1.00 (1.00, 1.00)
Working Memory								
ACE	2035.5	752	-	-	531.5	0.52 (0.25, 0.71)	0.11 (0.00, 0.32)	0.37 (0.29, 0.47)
AE	**2036.5**	**753**	**1.0**	**1**	**530.5**	**0.64 (0.55, 0.72)**	**-**	**0.36 (0.28, 0.45)**
CE	2049.6	753	14.1	1	543.6	-	0.46 (0.38, 0.54)	0.54 (0.46, 0.62)
E	2143.0	754	107.4	2	635.0	-	-	1.00 (1.00, 1.00)
Reasoning								
ACE	2008.2	749	-	-	510.2	0.46 (0.20, 0.68)	0.16 (0.00, 0.37)	0.38 (0.30, 0.48)
AE	**2010.3**	**750**	**2.0**	**1**	**510.3**	**0.63 (0.55, 0.70)**	**-**	**0.37 (0.30, 0.45)**
CE	2020.5	750	12.2	1	520.5	-	0.48 (0.40, 0.56)	0.52 (0.45, 0.60)
E	2130.7	751	122.5	2	628.7	-	-	1.00 (1.00, 1.00)

NOTE: RC = Relational Complexity, IQ =Full-scale IQ, WMem = Working Memory

[a]Best-fitting models shown in **bold**.

Table S5. Multivariate Model-Fitting Results (best-fitting model in **bold,** parameter estimates shown for best-fitting model) for Latin Square, N-term, and Sentence Tasks.

Model[a]	-2 log likelihood	df	AIC
1. Cholesky ACE	6051.391	2331	1389.4
2. Cholesky AE	**6052.943**	**2337**	**1378.9**
3. Cholesky CE	6075.994	2337	1402.0
4. Independent Pathway: 1xA Factor plus Specifics, Cholesky E	6056.261	2237	1382.3
5. Common Pathway: 1 Common Factor, plus specifics	6057.401	2339	1379.4

	Cholesky AE Model Parameters (shown as a %)							
	Additive Genetic Factors[b]			Total A	Unshared Environmental Factors[b]			
	A1	A2	A3	(h^2)	E1	E2	E3	Total E
Sentence	55 (45-64)	-	-	55	45 (36-55)	-	-	45
N-term	40 (29-51)	11 (03-21)	-	51	02 (0.1-05)	47 (39-56)	-	49
Latin Square	18 (05-29)	23 (07-36)	01 (00-18)	43	01 (00-04)	00 (00-0.1)	56 (46-67)	57

[a]The significance of additive genetic (A) and common environmental (C) influences were tested in a Cholesky model. While C could be dropped from the fully-saturated model without loss of fit ($\Delta\chi^2_6 = 1.6$; Model 2), dropping A resulted in a significant worsening of fit ($\Delta\chi^2_6 = 24.6$; Model 3). Therefore, a Cholesky model allowing for A and E, but not C influences (i.e. Model 2) was the most parsimonious and best-fitting Cholesky model. Retaining the AE format, independent and common pathway models were compared to the best-fitting Cholesky model. The AE Cholesky remained the best-fitting, although the fit of the common pathway model was almost identical (AIC = 1378.9 vs. 1379.4), and consequently, estimates are shown for both models (Cholesky in this Table and the common pathway, which is considered a more interpretable model [1], in Figure 2.
[b]Cholesky estimates on the diagonal include both common and specific influences (A1, A2, E1, E2) or specific influences only (A3, E3). Estimates on the off-diagonal represent common influences

References

1. Loehlin JC (1996) The Cholesky approach: A cautionary note. Behavior Genetics 26: 65-69.

Table S6. Top 50 Single Nucleotide Polymorphisms (SNPs)[a] for Relational Complexity (RC)

Chr	SNP	AL1	AL2	MAF (AL1)	Beta	SE	*p*-value	Gene	*p*-values in Related Traits		
									IQ	Reasoning	Working Memory
10	**rs4390263**	A	G	.449	-.348	.072	1.4×10^{-6}	near NPS[c]	2.4×10^{-2}	3.3×10^{-3}	4.5×10^{-2}
11	rs12807847	T	C	.058	.667	.152	1.2×10^{-5}	SLC5A12	6.4×10^{-3}	.080	.059
3	rs7625359	T	C	.106	-.496	.116	1.9×10^{-5}	-	.961	.133	.192
9	rs10820743	C	T	.303	-.302	.071	2.1×10^{-5}	ABCA1	.207	.152	.012
11	rs4755955	A	G	.176	-.415	.098	2.3×10^{-5}	-	3.1×10^{-2}	.147	.091
17	rs3606	A	G	.344	.319	.077	3.5×10^{-5}	SLC39A11	.488	4.9×10^{-2}	1.4×10^{-2}
9	rs722353	C	T	.175	.376	.091	3.7×10^{-5}	ZNF169	.098	2.9×10^{-2}	.320
14	**rs12882037**	T	C	.232	.356	.086	3.7×10^{-5}	-	3.7×10^{-2}	5.6×10^{-3}	2.2×10^{-2}
14	rs4982279	G	T	.209	.353	.086	4.4×10^{-5}	-	1.3×10^{-2}	$21.2x\ 10^{-3}$	.123
13	rs9567377	T	G	.117	-.436	.107	4.8×10^{-5}	-	.401	8.2×10^{-3}	1.0×10^{-3}
2	rs1905925	T	C	.485	.287	.071	5.5×10^{-5}	LRP1B	.263	1.3×10^{-3}	.064
20	rs2208981	C	T	.188	.346	.086	5.6×10^{-5}	-	.603	1.6×10^{-3}	4.4×10^{-2}
15	rs1565866	T	G	.440	.283	.070	5.7×10^{-5}	BUB1B	.063	5.8×10^{-2}	.134
15	rs1968813	A	C	.486	-.279	.070	6.4×10^{-5}	-	.091	1.1×10^{-3}	.094
2	rs17842284	A	G	.204	.343	.086	7.2×10^{-5}	-	.057	.224	.024
12	rs10777776	C	A	.374	.301	.076	7.4×10^{-5}	ELK3	.123	.161	3.2×10^{-2}
5	rs347721	T	C	.495	.279	.070	7.5×10^{-5}	CDH18	.798	3.4×10^{-2}	1.1×10^{-2}
9	rs12346832	C	T	.265	.318	.080	7.7×10^{-5}	-	.359	4.8×10^{-2}	4.6×10^{-2}
8	rs1499370	G	A	.381	.281	.071	7.7×10^{-5}	PVT1	.687	1.5×10^{-2}	.308
15	rs2175462	T	C	.290	-.317	.080	8.2×10^{-5}	-	.883	3.5×10^{-3}	1.9×10^{-3}
14	rs4561383	C	T	.167	.381	.097	8.6×10^{-5}	-	.060	.080	.220
11	rs12270727	T	G	.043	.699	.179	9.3×10^{-5}	SLC5A12	3.1×10^{-2}	.388	3.6×10^{-2}
17	rs7406894	T	C	.300	.295	.076	9.8×10^{-5}	-	.268	.332	.269
12	rs7315837	G	A	.204	-.353	.091	1.0×10^{-4}	-	.510	.107	8.9×10^{-4}
2	rs2724855	A	G	.381	.282	.073	1.0×10^{-4}	-	.057	5.5×10^{-3}	.420
17	rs4148418	G	A	.393	-.267	.069	1.1×10^{-4}	ANKRD40	.087	1.0×10^{-2}	.124
3	rs13079094	T	C	.324	-.289	.075	1.1×10^{-4}	-	.065	5.9×10^{-3}	1.1×10^{-2}
12	rs596940	C	T	.068	-.504	.131	1.2×10^{-4}	PITPNM2	3.5×10^{-2}	9.1×10^{-3}	.607
21	**rs3827183**	A	G	.128	-.406	.106	1.2×10^{-4}	DOPEY2	4.0×10^{-3}	3.1×10^{-5}	1.6×10^{-2}
17	rs757597	A	G	.440	.277	.072	1.2×10^{-4}	MYOCD	.437	2.8×10^{-2}	9.1×10^{-3}
4	rs1817186	A	G	.078	.569	.148	1.2×10^{-4}	-	.130	2.8×10^{-3}	3.1×10^{-2}
7	rs10243024	A	G	.248	-.328	.085	1.2×10^{-4}	MET	.137	1.3×10^{-2}	5.8×10^{-3}
16	rs1376047	T	C	.156	-.366	.095	1.2×10^{-4}	-	.167	.137	3.5×10^{-3}
1	rs4503375	G	A	.170	-.375	.098	1.3×10^{-4}	VAV3	.654	9.1×10^{-3}	1.9×10^{-2}
9	rs11791976	G	A	.058	-.605	.158	1.3×10^{-4}	-	.910	.142	.201
14	rs11624232	T	C	.164	.379	.099	1.3×10^{-4}	-	.157	2.3×10^{-2}	.058
21	rs2825236	C	T	.307	-.318	.083	1.4×10^{-4}	-	.608	.118	.874
9	rs273472	G	A	.432	-.272	.071	1.4×10^{-4}	-	.068	.126	1.2×10^{-2}
2	**rs10209999**	G	A	.229	-.303	.080	1.4×10^{-4}	-	3.3×10^{-2}	2.3×10^{-2}	8.0×10^{-3}
20	rs6109686	A	G	.151	.371	.098	1.4×10^{-4}	SPTLC3	4.1×10^{-2}	2.3×10^{-3}	.235
10	**rs11195283**	A	C	.293	-.281	.074	1.4×10^{-4}	RBM20	4.8×10^{-2}	1.4×10^{-2}	2.9×10^{-3}
8	**rs2442756**	C	A	.357	.282	.074	1.5×10^{-4}	VPS13B	2.5×10^{-4}	1.6×10^{-5}	4.1×10^{-2}
15	rs2665111	C	T	.296	.305	.080	1.5×10^{-4}	-	.342	4.1×10^{-3}	1.4×10^{-4}
17	rs792766	A	G	.400	.276	.073	1.5×10^{-4}	-	.066	.069	.661
17	rs1990293	A	G	.191	.344	.091	1.5×10^{-4}	BCAS3	.750	3.4×10^{-3}	.565
9	rs10821076	A	G	.479	.259	.068	1.5×10^{-4}	-	.084	1.4×10^{-2}	.054
2	rs1531078	T	G	.201	.357	.094	1.5×10^{-4}	-	.330	.081	.263
9	rs182719	A	G	.111	-.427	.113	1.6×10^{-4}	PTPRD	.190	4.6×10^{-2}	.160
2	rs6725328	G	A	.190	-.327	.087	1.6×10^{-4}	-	.311	2.3×10^{-5}	1.3×10^{-2}
13	rs1323103	G	A	.364	-.272	.072	1.7×10^{-4}	-	.823	8.9×10^{-3}	5.1×10^{-3}

[a]Retained if LD threshold < .5
[b]GWAS p-value < 0.05. Shown in **red** if at least nominally significant for all traits.
[c]Intronic SNP, downstream of NPS (dist=3.62kb), LD = .6

Table S7. Top 50 Single Nucleotide Polymorphisms (SNPs)[a] for IQ

Chr	SNP	AL1	AL2	MAF (AL1)	Beta	SE	*p*-value	Gene	*p*-values in Related Traits		
									Relational Complexity	Reasoning	Working Memory
14	rs1242923	T	C	.388	-.165	.036	4.8×10^{-6}	ABHD4	.121	.711	.911
2	rs4438512	G	A	.442	-.153	.034	8.8×10^{-6}	ZNF638	.135	.187	.168
3	rs6777812	T	C	.239	-.179	.041	1.0×10^{-5}	COLQ	.091	.414	.511
10	rs2804164	T	C	.229	-.175	.040	1.2×10^{-5}	ATRNL1	.826	.786	.407
6	rs1570086	T	C	.426	-.152	.035	1.2×10^{-5}	-	.258	.173	.615
5	rs152642	G	T	.139	-.218	.050	1.3×10^{-5}	-	1.2×10^{-2}	6.3×10^{-3}	.293
7	rs4333513	T	C	.231	-.177	.041	1.4×10^{-5}	-	.398	.635	.694
4	rs1055263	A	G	.188	.193	.045	1.5×10^{-5}	-	3.7×10^{-3}	.062	.235
15	**rs4482248**	A	G	.223	-.177	.041	1.7×10^{-5}	-	1.8×10^{-3}	4.2×10^{-5}	3.3×10^{-3}
11	rs2851682	G	A	.087	.265	.062	2.0×10^{-5}	FADS2	.138	1.8×10^{-2}	.201
22	rs2023635	G	A	.308	-.158	.037	2.3×10^{-5}	-	.220	.139	.662
18	rs948699	A	C	.051	-.346	.082	2.3×10^{-5}	-	.298	.171	.137
6	rs4035344	G	A	.129	.213	.051	2.7×10^{-5}	C6orf211	.106	.185	.203
1	rs1726672	T	C	.289	.163	.039	2.8×10^{-5}	-	.725	.323	.416
11	**rs12419146**	A	C	.042	.370	.089	3.0×10^{-5}	PRR5L	6.2×10^{-4}	3.1×10^{-4}	2.5×10^{-3}
5	rs247456	C	T	.171	.187	.045	3.4×10^{-5}	-	4.4×10^{-2}	.129	.604
7	rs13242229	C	T	.307	-.158	.038	3.4×10^{-5}	DGKB	.126	7.8×10^{-3}	6.1×10^{-3}
21	rs3746882	C	T	.125	.221	.053	3.5×10^{-5}	ETS2	.342	.153	.768
16	rs7201962	G	A	.247	.164	.040	3.6×10^{-5}	-	.131	.541	.649
6	rs2496509	A	C	.350	.151	.037	3.8×10^{-5}	RIMS1	.772	.500	.832
5	rs7726354	T	C	.053	.329	.080	4.1×10^{-5}	-	.795	.733	.812
7	**rs7801010**	C	T	.276	.159	.039	4.5×10^{-5}	DGKB	5.3×10^{-3}	5.1×10^{-3}	1.7×10^{-2}
1	rs1436750	A	G	.071	-.269	.067	5.5×10^{-5}	CACHD1	.074	.054	.455
19	rs12460133	G	T	.261	.153	.038	5.6×10^{-5}	-	.343	.816	.814
20	rs804544	C	A	.067	.289	.072	5.8×10^{-5}	-	.125	1.9×10^{-2}	3.8×10^{-2}
5	rs9292673	G	A	.168	-.185	.046	5.8×10^{-5}	-	.410	3.8×10^{-2}	.051
7	rs4909242	G	A	.098	-.237	.059	6.1×10^{-5}	PTPRN2	.294	2.6×10^{-2}	.731
4	rs10031105	C	T	.200	-.173	.043	6.1×10^{-5}	-	.623	.723	.914
2	rs7592135	A	G	.369	.140	.035	6.1×10^{-5}	-	.662	.112	.222
2	rs10932241	C	A	.400	-.140	.035	6.4×10^{-5}	-	4.2×10^{-2}	.541	.615
6	rs12524770	T	C	.281	-.158	.039	6.5×10^{-5}	-	.067	3.4×10^{-3}	.395
5	rs17842609	A	C	.051	.310	.078	6.7×10^{-5}	-	.105	.196	.955
5	**rs2964546**	T	C	.332	.148	.037	6.7×10^{-5}	-	1.8×10^{-2}	4.4×10^{-2}	2.6×10^{-2}
14	rs11157695	G	A	.387	-.142	.036	6.7×10^{-5}	ABHD4	.346	.595	.278
6	rs311232	T	C	.176	-.181	.045	6.7×10^{-5}	BEND3	.101	1.9×10^{-2}	.105
14	rs17254544	A	G	.198	.176	.044	6.8×10^{-5}	-	.242	.164	.407
6	rs2791333	G	A	.384	.142	.036	7.2×10^{-5}	ZNF192	.460	.285	.846
7	rs17170988	C	A	.197	-.174	.044	7.4×10^{-5}	ELMO1	.886	.590	.677
5	rs17386472	T	C	.089	-.248	.063	7.5×10^{-5}	GDNF	.606	.997	.175
14	rs17128136	A	G	.075	-.265	.067	7.6×10^{-5}	SOCS4	.063	.050	.072
19	rs11672523	G	A	.115	-.210	.053	7.7×10^{-5}	SPTBN4	.057	1.7×10^{-3}	6.7×10^{-3}
1	rs12116428	T	C	.070	-.261	.066	7.9×10^{-5}	-	.616	.805	.382
18	rs9944757	T	G	.090	.241	.061	8.3×10^{-5}	-	.391	.614	.196
6	rs7765204	G	A	.318	-.145	.037	8.4×10^{-5}	-	.116	.609	.286
4	rs317892	A	G	.213	-.170	.043	8.9×10^{-5}	-	.113	.383	.551
1	rs963208	T	C	.352	-.141	.036	9.2×10^{-5}	-	.157	4.9×10^{-2}	.346
18	rs7233676	T	C	.363	.140	.036	9.2×10^{-5}	-	.655	.072	.766
3	rs2455826	T	G	.276	-.152	.039	9.3×10^{-5}	BTD	.815	.828	.548
1	rs3767004	A	G	.073	-.270	.069	9.6×10^{-5}	CACNA1E	.812	.843	.616
15	rs16967271	A	G	.055	.283	.073	1.0×10^{-4}	-	.174	.393	.499

[a]Retained if LD threshold < .5

[b]GWAS p-value < 0.05. Shown in **red** if at least nominally significant for all traits.

Table S8. Minor Allele Frequencies for Follow-Up Single Nucleotide Polymorphisms (SNPs) in Discovery and Replication Samples

Chr	SNP	Effect Allele	Non-Effect Allele	Minor Allele Frequency				
				Australian Discovery	Norwegian NCNG	Scottish LBC1936	Dutch NTR	English ALSPAC
2	rs10209999	G	A	0.229	0.236	0.234	-	0.232
5	rs2964546	T	C	0.332	0.299	0.317	0.311	0.328
7	rs7801010	C	T	0.276	0.309	0.284	0.274	0.275
8	rs2442756	C	A	0.357	0.326	0.400	0.392	0.363
10	rs11195283	A	C	0.293	0.285	0.301	0.326	0.286
10	rs4390263	A	G	0.449	0.453	0.474	0.482	0.468
11	rs12419146	A	C	0.042	0.030	0.045	0.034	0.042
14	rs1242923	T	C	0.388	0.409	0.399	0.390	0.386
14	rs12882037	T	C	0.232	0.260	0.232	0.223	0.224
15	rs4482248	A	G	0.223	0.232	0.228	0.222	0.230
21	rs3827183	A	G	0.128	0.102	0.121	0.147	0.123

Table S9. Association Results for Six Loci Selected for Replication from the Relational Complexity (RC) Genome-Wide Association Analysis

	rs10209999 (*intergenic*, Chr 2)			rs2442756 (*VPS13B*, Chr 8)			rs11195283 (*RBM20*, Chr 10)			rs4390263[a] (*near NPS*, Chr 10)			rs12882037 (*intergenic*, Chr 14)			rs3827183 (*DOPEY2*, Chr 21)		
	P value	**β**	**SE**	**P value**	**β**	**SE**	**P value**	**β**	**SE**	**P value**	**β**	**SE**	**P value**	**β**	**SE**	**P value**	**β**	**SE**
Discovery Sample (N ranges 481-1999 (234-894 families))																		
RC	***1.4x10^{-4}***	-0.30	0.08	***1.5x10^{-4}***	0.28	0.07	***1.4x10^{-4}***	-0.28	0.07	***1.4x10^{-6}***	-0.35	0.07	***3.7x10^{-5}***	0.36	0.09	***1.2x10^{-4}***	-0.41	0.11
IQ	***0.033***	-0.09	0.04	***2.5x10^{-4}***	0.13	0.04	***0.048***	-0.07	0.04	***0.024***	-0.08	0.04	***0.037***	0.09	0.04	***4.0x10^{-3}***	-0.15	0.05
Reasoning	***0.023***	-0.19	0.08	***1.6x10^{-5}***	0.33	0.08	***0.014***	-0.19	0.08	***3.3x10^{-3}***	-0.21	0.07	***5.6x10^{-3}***	0.24	0.09	***3.1x10^{-5}***	-0.44	0.11
Working Memory	***8.0x10^{-3}***	-0.21	0.08	***0.041***	0.15	0.07	***2.9x10^{-3}***	-0.22	0.07	***0.045***	-0.014	0.07	***0.022***	0.20	0.09	***0.016***	-0.25	0.10
English ALSPAC (N=4078 unrelated)																		
IQ	0.765	0.01	0.03	0.845	-0.01	0.02	0.534	0.02	0.02	0.856	-0.004	0.02	0.684	-0.01	0.03	0.754	-0.01	0.03
Matrix Reasoning	0.584	-0.01	0.03	0.354	0.02	0.02	0.888	-0.004	0.02	0.877	0.004	0.02	0.491	0.02	0.03	0.630	-0.02	0.03
Scottish LBC1936 ((N=1001 unrelated)																		
Moray House (IQ)	0.503	0.02	0.03	0.134	-0.05	0.03	0.203	-0.04	0.03	***0.041***	0.07	0.03	0.322	0.03	0.03	0.434	-0.02	0.03
Matrix Reasoning	0.884	-0.005	0.03	0.861	0.01	0.03	0.806	-0.01	0.03	***9.5x10^{-3}***	0.08	0.03	0.780	-0.01	0.03	0.750	0.01	0.03
Letter Number Sequence	0.847	0.01	0.03	0.268	-0.04	0.03	0.445	-0.02	0.03	**0.098**	0.05	0.03	0.663	0.01	0.03	0.716	-0.01	0.03
Dutch NTR (N=920 (340 families))																		
Raven's Prog. Matrices	-	-	-	0.162	-0.08	0.05	0.144	0.08	0.05	0.400	0.04	0.05	0.150	0.10	0.07	0.252	-0.09	0.08
Norwegian NCNG (N=670 unrelated)																		
IQ	0.210	-0.88	0.70	0.32	-0.63	0.63	0.129	0.99	0.65	**0.070**	1.08	0.59	**0.058**	-1.25	0.66	***0.029***	2.13	0.97
Matrix Reasoning	***0.045***	-0.52	0.26	***0.020***	-0.55	0.23	**0.096**	0.40	0.24	**0.081**	0.39	0.22	0.225	-0.30	0.24	0.128	0.55	0.36
Letter Number Span	0.106	-0.35	0.21	0.736	-0.06	0.19	0.157	0.28	0.20	0.512	-0.12	0.18	**0.095**	-0.33	0.20	***3.0x10^{-3}***	0.88	0.30
Digit Symbol	0.699	0.27	0.69	0.834	-0.13	0.62	0.475	-0.46	0.64	***2.0x10^{-3}***	1.81	0.58	0.268	0.72	0.65	0.310	-0.98	0.96

Combined Samples

Meta-analyses (IQ: N=7083 unrelated, Reasoning: N=6570 unrelated, Working Memory: N=1825 unrelated)

	P value	**z-score**	**P value**	**z-score**	**P value**	**z-score**	**P value**	**z-score**	**P value**	**z-score**	**P value**	**z-score**
IQ[b]	0.489	-0.693	0.755	0.312	0.791	-0.265	0.696	0.391	0.805	0.247	0.352	-0.931
Reasoning[c]	**0.052**	-1.943	0.637	0.472	0.943	-0.071	0.322	0.991	0.676	-0.419	0.417	-0.812
Working Memory[d]	0.558	-0.586	0.621	-0.495	0.496	-0.681	***0.023***	2.270	**0.076**	1.775	**0.088**	-1.710
	(**0.092**)	(-1.687)	(0.789)	(0.267)	(0.346)	(-0.943)	(0.385)	(0.869)	(0.762)	(0.303)	(0.690)	(0.399)

NOTE: P values <0.05 are shown in bold and underlined, while those >0.05 but <0.10 are shown in bold only. At a gene-based level, in the Discovery sample, *NPS* was the top ranked gene (p=1.5x10^{-5}) for RC, while *VPS13B* and *DOPEY2* were nominally associated (p=0.02, 0.04 respectively). *RBM20* was not a VEGAS-listed gene. Traits are standardised (z-scores, M=0±1) for all cohorts excepting NCNG.

[a] The top-ranked loci for RC was rs4390263.

[b]Meta-analysis for IQ included the following measures: Discovery - IQ (5 subtests of the Multidimensional Aptitude Battery), ALSPAC and NCNG - IQ (2 subtests of the WASI - includes Matrix Reasoning); LBC1936 - Moray House

[c]Meta-analysis for reasoning included the following measures: Discovery – RC; ALSPAC/LBC1936/NCNG - Matrix Reasoning; NTR - Raven's Progressive Matrices

[d]Meta-analysis for working memory included the following measures: Discovery – Working Memory component; LBC1936 – Letter Number Sequence; NCNG – Digit Symbol (results using Letter Number Span are shown in brackets)

Table S10. Association Results for Four Loci Selected for Replication from the IQ Genome-Wide Association Analysis

	rs2964546 (*intergenic*, Chr 5)			rs7801010 (*DGKB*, Chr 7)			rs12419146 (*PRR5L*, Chr 11)			rs1242923[a] (*ABHD4*, Chr 14)			rs4482248 (*intergenic*, Chr 15)		
	P value	**β**	**SE**	**P value**	**β**	**SE**	**P value**	**β**	**SE**	**P value**	**β**	**SE**	**P value**	**β**	**SE**
Discovery Sample (N ranges 481-1999 (234-894 families))															
IQ	***6.7x10^{-5}***	0.15	0.04	***4.5x10^{-5}***	0.16	0.08	***3.0x10^{-5}***	0.37	0.09	***4.8x10^{-6}***	-0.17	0.04	***1.7x10^{-5}***	-0.18	0.04
Relational Complexity	***0.018***	0.17	0.07	***5.3x10^{-3}***	0.22	0.08	***6.2x10^{-4}***	0.57	0.17	0.121	0.11	0.07	***1.8x10^{-3}***	-0.26	0.08
Reasoning	***0.044***	0.15	0.07	***5.1x10^{-3}***	0.22	0.08	***5.3x10^{-4}***	0.62	0.17	0.711	-0.17	0.07	***4.2x10^{-5}***	-0.35	0.09
Working Memory	***0.026***	0.16	0.07	***0.017***	0.18	0.08	***2.5x10^{-3}***	0.51	0.17	0.911	0.01	0.07	***3.3x10^{-3}***	-0.24	0.08
English ALSPAC (N=4078 unrelated)															
IQ	0.139	0.04	0.02	0.941	-0.002	0.03	0.993	-0.001	0.06	0.489	-0.02	0.02	***0.021***	-0.06	0.03
Matrix Reasoning	0.112	-0.04	0.02	0.636	-0.01	0.03	0.881	-0.01	0.06	0.814	-0.005	0.02	**0.062**	0.05	0.03
Scottish LBC1936 (N=1001 unrelated)															
Moray House (IQ)	0.402	-0.03	0.03	**0.060**	0.06	0.03	***0.041***	0.07	0.03	0.766	-0.01	0.03	0.776	0.01	0.03
Matrix Reasoning	0.112	-0.05	0.03	0.603	0.02	0.03	0.980	0.001	0.03	0.762	-0.01	0.03	0.766	0.01	0.03
Letter Number Sequence	0.597	-0.02	0.03	0.763	0.01	0.03	0.134	0.05	0.03	0.383	0.03	0.03	0.442	-0.02	0.03
Dutch NTR (N=920 (340 families))															
Raven's Prog. Matrices	0.992	-0.001	0.06	0.281	-0.07	0.06	0.664	0.06	0.14	0.945	0.004	0.06	***7.2x10^{-3}***	0.22	0.08
Norwegian NCNG (N=670 unrelated)															
IQ	0.346	0.62	0.64	0.851	-0.12	0.64	0.554	1.03	1.74	**0.051**	1.15	0.59	0.943	0.05	0.70
Matrix Reasoning	0.229	0.29	0.24	***0.028***	0.52	0.24	0.282	-0.70	0.65	0.296	0.23	0.22	0.220	0.32	0.26
Letter Number Span	0.141	0.28	0.19	0.497	-0.13	0.19	**0.061**	-0.95	0.51	0.746	0.06	0.18	0.741	0.07	0.20
Digit Symbol	0.349	0.60	0.64	0.565	-0.36	0.63	0.359	-1.60	1.69	0.621	-0.29	0.59	0.289	-0.73	0.69

Combined Samples
Meta-analyses (IQ: N=7083 unrelated, Reasoning: N=6570 unrelated, Working Memory: N=1825 unrelated)

	P value	**z-score**	**P value**	**z-score**	**P value**	**z-score**	**P value**	**z-score**	**P value**	**z-score**
IQ[b]	***9.0x10^{-3}***	2.613	***0.033***	2.135	**0.057**	1.900	**0.082**	-1.739	***1.1x10^{-3}***	-3.264
Reasoning[c]	0.437	-0.777	0.798	0.256	0.756	0.310	0.729	0.346	***0.042***	2.030
Working Memory[d]	0.345	1.201	0.456	0.755	**0.096**	1.277	0.688	0.880	***0.026***	-1.503
	(0.230)	(0.945)	(0.450)	(0.745)	(0.202)	(1.664)	(0.379)	(0.402)	(0.133)	(-2.226)

NOTE: P values <0.05 are shown in bold and underlined, while those >0.05 but <0.10 are shown in bold only. At a gene-based level, in the Discovery sample, the genes *DGKB* and *ABHD4* were nominally associated with IQ (p=0.03, 8.1x10^{-4} respectively). *PRR5L* was not a VEGAS-listed gene. Traits are standardised (z-scores, M=0±1) for all cohorts excepting NCNG.

[a] The top-ranked loci for IQ was rs1242923.

[b]Meta-analysis for IQ included the following measures: Discovery - IQ (5 subtests of the Multidimensional Aptitude Battery), ALSPAC and NCNG - IQ (2 subtests of the WASI - includes Matrix Reasoning); LBC1936 - Moray House

[c]Meta-analysis for reasoning included the following measures: Discovery – RC ; ALSPAC/LBC1936/NCNG - Matrix Reasoning; NTR - Raven's Progressive Matrices

[d]Meta-analysis for working memory included the following measures: Discovery – Working Memory component; LBC1936 – Letter Number Sequence; NCNG – Digit Symbol (results using Letter Number Span are shown in brackets)

Table S11. Gene Function.

SNP	Gene	Location	Gene Function
(Top ranked gene for IQ)	*FAM105A*	5p15.2	*FAM105A* (family with sequence similarity 105, member A): This is a proapoptotic gene not as yet well characterised [1].
rs7801010	*DGKB*	7p21.2	*DGKB* (diacylglycerol kinase, beta 90kDa): The diacylglycerol kinases have key roles in regulating many intracellular signalling proteins and are implicated in a range of human pathologies [2] including brain afflictions (e.g. *DGKH* with bipolar disorder and ***schizophrenia*** [3]). In addition, there are plausible links with cognitive function. Rat studies show that DGKB is an important modulator of protein kinase C [4], which is crucial for ***hippocampal memory formation*** [5]. Consistent with this finding, they also show DGKB involvement in dendritic spine shape and maturation in developing ***hippocampal neurons***, with flow-on effects for ***cognitive processes including memory*** [6,7]. Although little is known regarding the functional significance of multiple human *DGKB* isoforms, it has been suggested that altered relative levels of particular transcripts may influence emotional and ***cognitive behaviour*** by altering diacylglycerol turnover in the amygdala, caudate nucleus, and ***hippocampus*** [4]. More recently, *DGKB* was associated with fasting glucose homeostasis and type 2 diabetes in GWA meta-analyses [8] with a subsequent study finding it associated with insulin secretion [9]. Insulin has a profound effect on the brain, with insulin resistance underlying multiple chronic conditions known to impact ***cognitive function*** [10]. Gene-based tests in independent Norwegian (NCNG) and British (CAGES) samples, both of which contribute to the current association meta-analyses (Table S12), found suggestive evidence that the gene *DGKB* influences ***fluid intelligence*** ($p = 0.04$ and 0.001 respectively[11]). The current GWA meta-analyses suggested the minor allele of rs7801010 was associated with better cognitive ability.
rs2442756	*VPS13B*	8q22.2	*VPS13B* (vacuolar protein sorting 13 homolog B (yeast)) is a large multiexonic gene that shows alternative splicing. It has a broad expression pattern and is expressed differentially in the brain compared to other tissues (i.e. the major brain transcript (variant 1) is not the main form in other tissues [12]). It is proposed that alternative splicing may be of central importance for genes involved in information processing functions with the majority of alternative spliced genes found to be functionally involved in transmitting and regulating signals [13]. Mutations in the gene have been linked to Cohen syndrome [14], for which features include ***microcephaly (small head size)*** and moderate to severe ***intellectual impairment*** [15]. However, detailed gene function remains to be determined. In GWA meta-analyses conducted by the ENIGMA consortium (N=21,151) [16], the major allele of rs2442756 was associated with ***reduced hippocampal volume*** ($p = 0.018$) – for sample overlap see Table S12. The current GWA analyses suggested the major allele of rs2442756 was associated with worse relational processing ability in the Discovery sample, but the finding was not supported in the replication cohorts.
rs11195283	*RBM20*	10q25.2	Mutations in *RBM20* (RNA binding motif protein 20) have been associated with atrial fibrillation [17] and advanced disease in patients with dilated cardiomyopathy [18]. Atrial fibrillation is reported to be a determinant of low ***cognitive function*** in elderly men [19] and is associated with poorer ***cognitive outcomes*** in stroke patients [20,21]. The current GWA analyses suggested the minor allele of rs11195283 was associated with worse relational processing ability in the Discovery sample, but the finding was not supported in the replication cohorts.
rs4390263 (Plus: Top ranked gene for RC)	*NPS*	10q26.2	rs4390263 is 3.62 kb downstream of *NPS* (neuropeptide S) in a block of moderate linkage disequilibrium that extends from the beginning of the gene. NPS was first characterised in rodents as a modulator of sleep-wake cycles and anxiety [22]. With NPSR1 (neuropeptide S receptor 1), NPS forms a signalling system that has been implicated in susceptibility to multiple disorders in humans, including ***schizophrenia*** [23], panic disorder [24], and anxiety [25]. The NPSR1-NPS system is reported to modulate ***verbal memory*** consolidation in ***schizophrenia patients*** [23], consistent with a finding in mice whereby central NPS administration was able to dose dependently enhance ***memory retention*** [26]. In addition, it has been associated with activation levels in the dorsolateral prefrontal cortex (during the processing of fearful faces [24]), and in this capacity, it may also influence relational processing and working memory, which are known to engage this brain region [27,28]. In certain paradigms, it shows a pharmacological profile similar to clozapine (an atypical antipsychotic ***schizophrenia*** medication) and may be a potentially useful treatment for ***schizophrenia*** [29]. While results are as yet inconclusive, clozapine has been examined as a potential treatment of ***cognitive deficits associated with schizophrenia***, including verbal and visual learning, working memory, reasoning, and processing speed

			[see review 30]. In GWA meta-analyses by the Psychiatric Genomics Consortium (N=51,695) [31], rs4390263 was nominally associated with ***schizophrenia*** (p = 0.022), with the minor allele being protective. The current GWA meta-analyses suggested the minor allele was associated with better working memory performance.
rs12419146	*PRR5L*	11p13-p12	*PRR5L* (proline rich 5 like) is reported to play a role in regulating mRNA stability [32]. The current GWA meta-analyses suggested the minor allele of rs12419146 was associated with better cognitive ability.
rs1242923	*ABHD4*	14q11.2	Rodent studies suggest that *Abhd4* (abhydrolase domain containing 4) plays a role in the biosynthesis of endocannabinoids [33,34] and that endocannabinoid signalling is involved in ***learning and memory***. Multiple lines of evidence demonstrate that the system is involved in ***schizophrenia*** pathology (see review [35]). The current GWA meta-analyses suggested the minor allele of rs1242923 was associated with worse cognitive ability.
rs12882037	*ESRRB*	14q24.3	rs12882037 is 20.5 kb upstream of *ESRRB* (estrogen-related receptor beta) in a block of high linkage disequilibrium (0.8) that partly overlaps with the gene. Studies in mice suggest that Errb affects body composition, neuropeptide levels, stress hormones, and centrally-modulated startle responses [36]. Abnormal startle responses are found in ***schizophrenia*** patients [37] and have been investigated as an indicator of attention-dependent ***cognitive deficits*** [38,39]. The current GWA analyses suggested the minor allele of rs12882037 was associated with better relational processing ability in the Discovery sample, but the finding was not supported in the replication cohorts.
rs2837183	*DOPEY2*	21q22.2	*DOPEY2* (dopey family member 2) is a highly conserved gene containing leucine zipper-like domains with protein-protein interaction functions [40,41]. Studies suggest a conserved function in the control of morphogenesis (i.e. shapes of tissues, organs, entire organisms, and positions of the various specialised cell types), with a role in human morphogenesis of the cortex [40]. It is widely expressed in embryonic human CNS, but later in development, in the fetal brain, it becomes restricted to the cortex, cerebellum, and ***hippocampal formation*** – regions associated with ***learning and memory***, and regions where in Down syndrome, it is overexpressed, consistent with its location in the Down Syndrome Critical Region on chromosome 21 [42,43]. Thus, it is proposed as a candidate gene for a number of neurological alterations found in Down syndrome (i.e. ***hypoplasia of the hippocampus*** and cortex, smaller cerebellum, and ***mental retardation***). The current GWA analyses suggested the minor allele of rs2837183 was associated with worse relational processing ability in the Discovery sample, but the finding was not supported in the replication cohorts.

NOTE: Terms associated with cognitive function (including the hippocampus - a brain region commonly associated with memory function [44]) and with psychopathology are underlined and shown in bold with italcs.

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Table S12. Sample Overlap Between Current Association and Previous Genome-Wide Association Meta-Analyses of Cognitive and Related Phenotypes

	Number of Participants				
	Adult Cognition [1,2]	Childhood Cognition [3]	Educational Attainment [4]	Hippocampal Volume [5]	Schizophrenia [6]
Discovery Sample	-	1725	-	485	-
ALSPAC[a]	-	4078	-	-	-
LBC1936	1005	947	1005	249	-
NTR	-	739[b]	183	-	-
NCNG	670	-	-	327	-

[a]Parental data contributed to Educational Attainment
[b]Replication sample.

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Text S1. Relational Complexity Tasks: each contained items at two (ternary- and quaternary-relational) or three (binary- ternary- and quaternary-relational) levels of complexity and assessed relational processing in different content domains [1]. Computer presentation of each of the tasks provided both instruction and automatic timing and scoring, and ensured task conformity. For each task the main dependent measure was accuracy and no time limits were imposed.

(A) The **Sentence Comprehension** task required processing of the noun-verb relations. It was adapted from Andrews et al. [1] and comprised a total of 22 sentences containing relative clauses. There were Subject-relative and Object-relative sentences, each requiring either 3 or 4 role assignments. Sentences were presented one at a time on the screen. Participants were asked to read each sentence carefully and when they understood the sentence, to move to a probe question (at which time the sentence could no longer be seen) and select their answer from the options available. The probe question assessed comprehension by asking about a noun-verb relation, such as "who (action specified)?", or "what did (specified person) do?". Of the 22 sentences, six were subject relative and 16 object-relative with 50% of sentences requiring processing of 3-role noun-verb relationships and 50% requiring 4-role assignments. These 4 sentence types (subject, object relative; 3-, 4-role) were randomized and presented in the same order for each participant. Instructions were given on the screen, with the opportunity to address questions to a research assistant if necessary. The task was scored by summing the number of correct responses, with a maximum score of 22.

(B) The **N-term** task is an extended version of a transitive inference task and was adapted from Andrews et al. [1]. In this task, relationships are inferred from the premises provided and thus inferential reasoning is required. In the 4-term example, the premises consist of a set of 4 paired letters, with the relationship between the letters indicated by a combination of greater than (>) and less than (<) signs (e.g. B > A) Participants are instructed to order the letters from greatest to smallest according to the information in the premises, and to construct the entire sequence mentally before beginning to type the sequence into the boxes. Once a letter has been entered participants are unable to reorder them. The premise information contained two levels of complexity: 3-term and 4-term items, with 8 trials presented for each complexity level using a blocked design. Each block was preceded by an example and one practice item, after which, participants had the opportunity to ask questions if anything was unclear. In scoring responses as correct or incorrect, relationship rather than direction was taken as the key element. Thus where participants confused the "<" and ">" signs, answers that were in the reverse of the correct order (i.e. that were ordered from smallest to greatest) were deemed to be correct. The task was scored by summing the number of correct sequences, with a maximum score of 16.

(C) The **Latin Square** task was adapted from Birney et al. [2,3]. It comprises a 'problem square' consisting of a 4×4 matrix, with each cell either containing one of four shapes or no shape (i.e. remaining empty). The task was to determine which shape, selected from an 'option' panel, should occur in a specified cell (indicated by a question mark). In the 'completed square', each shape should occur only once in each row and each column. Three practice trials of increasing complexity were presented, with a research assistant explaining and guiding the participant on how the correct response is determined. Participants were instructed to work through the problems as quickly as possible without sacrificing accuracy, and to do all the work in their heads. A total of 12 problems divided equally between 3 complexity levels (binary-relational, ternary-relational, and quaternary-relational) were then presented.

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Text S2. Structural Equation Modelling. Figures 2-3 show variance and covariance partitioned into additive genetic (A) and non-shared environmental (E) sources of variance.

Figure 2 (common pathway model [1]) shows that genetic sources accounted for 41-57% of the variance in the individual tasks (i.e. heritability (h^2) ranged 0.41-0.57). The latent relational processing factor was highly heritable (86%) and accounted for all of the genetic variance in the N-term Task (i.e. $(0.93^2 x 0.79^2)/0.54$), 72% for the Sentence Task, and 69% for Latin Square. In contrast, unique environmental influences were mainly specific to each variable with specific influences (E_S) accounting for 83-92% of total environmental variance (e.g. Sentence Task = 37/(100-57). This model confirms a strong latent factor and shows that it is largely genetic in nature. Heritability was maximised as the factor is free of uncorrelated measurement error, which is partitioned into the specific environmental (E_S) pathways.

Figure 3 (Cholesky decomposition [1]) partitioned covariation between RC, IQ, Reasoning and Working Memory into additive genetic (A) and non-shared environmental sources (E). The genetic source influencing RC (A_1) accounted for 59% of genetic variance in IQ (50/85), 69% for Reasoning (44/64), and 39% for Working Memory (25/64). For more detail regarding covariation between RC and IQ see Figure S2. Genetic sources (A_1, A_2, A_3) accounted for 89% of covariation between the traits Reasoning and Working Memory (r_p=0.52) (using tracing rules of path analysis [2,3]: ((0.67x0.50)+(0.30x0.16)+(0.32x0.25))/0.52), with unique environment accounting for the remaining 11%. Further, the covariation between Reasoning and Working Memory was largely influenced by sources also influencing RC. These accounted for 67% of the total (((0.67x0.50)+(0.11x0.10))/0.52) and 72% of the genetic covariation ((0.67x0.50)/((0.67x0.50) +(0.30x0.16)+(0.32x0.25))). Alternatively, of the covariation associated with RC, 97% was genetic. Independent of RC, IQ accounted for 12% of the total covariation (((0.30x0.16)+(0.21x0.07))/0.52) between Reasoning and Working memory and 10% of the genetic covariation ((0.30x0.16)/((0.67x0.50)+(0.30x0.16)+(0.32x0.25))). Note that due to the substantial overlap between RC and IQ, if IQ is allowed priority, it accounts for 75% of the genetic covariation between Reasoning and Working Memory, while RC independently accounts for a further 8%. All of the above multivariate analyses allowed for only A and E sources of influence as common environmental sources could be dropped at the univariate level (Table S4).

References

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